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GREIG I.
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The Oxford Handbook *of* NEUROLINGUISTICS

THE OXFORD HANDBOOK OF

NEUROLINGUISTICS

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Edited by

GREIG I. DE ZUBICARAY

and

NIELS O. SCHILLER

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PREFACE

GREIG I. DE ZUBICARAY AND NIELS O. SCHILLER

NEUROLINGUISTICS is a highly interdisciplinary field, with influences from psycholinguistics, psychology, aphasiology, (cognitive) neuroscience, and many more. A precise definition is elusive, but often neurolinguistics is considered to cover approximately the same range of topics as psycholinguistics, that is, all aspects of language processing, but approached from various scientific perspectives and methodologies. Twenty years ago, when the first *Handbook of Neurolinguistics*, edited by Harry Whitaker and Brigitte Stemmer, was published, it was relatively easy to identify the contributions from individual disciplines, with the dominant evidence base and approach being clinical aphasiology. Today, neurolinguistics has progressed such that individual researchers tackle topics of interest using multiple methods, and share a common sense of identity and purpose, culminating in their own society and annual conference. The *Society for the Neurobiology of Language* will have its tenth anniversary in 2018, and its annual meeting now regularly exceeds 700 attendees.

When we first proposed to collate and edit this *Handbook* of 35 chapters, we knew we were undertaking a challenging task given the rapid expansion of the field and pace of progress in recent years. We envisaged a mix of chapters from established and emerging researchers, with contributions covering the contemporary topics of interest to the field of neurolinguistics. We wanted more than the mere acknowledgment of the multilingual brain featured in previous handbooks, and to encourage varied perspectives on how language interacts with broader aspects of cognition and emotion. Responses to our invitations were mostly generous. By and large, we believe we have achieved much of what we set out to accomplish.

The scope and aim of this new *Oxford Handbook of Neurolinguistics* is to provide students and scholars with concise overviews of the state of the art in particular topic areas, and to engage a broad audience with an interest in the neurobiology of language. The chapters do not attempt to provide exhaustive coverage, but rather present discussions of prominent questions posed by a given topic.

Following an introductory chapter providing a brief historical perspective of the field, Part I covers the key techniques and technologies used to study the neurobiology of language today, including lesion-symptom mapping, functional imaging, electrophysiology, tractography, and brain stimulation. Each chapter provides a concise overview of the use of each technique by leading experts, who also discuss the various challenges that neurolinguistic researchers are likely to encounter.

Part II addresses the neurobiology of language acquisition during healthy development and in response to challenges presented by congenital and acquired conditions. Part III covers the many facets of our articulate brain, its capacity for language production—written, spoken, and signed—again from both healthy and clinical perspectives. Questions regarding how the brain organizes and represents meaning are addressed in Part IV, ranging from word to discourse level in written and spoken language, from perception to statistical modeling. The final Part V reaches into broader territory, characterizing and contextualizing the neurobiology of language with respect to more fundamental neuroanatomical mechanisms.

Our thanks go to the authors of the chapters, without whom the *Handbook* would not have been possible. Their commitment, expertise, and talent in exposition are rivaled only by their patience with the editorial process. Thanks also go to Peter Ohlin, Hannah Doyle, and Hallie Stebbins at Oxford University Press, who encouraged and ensured the publication of *The Oxford Handbook of Neurolinguistics*.

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David Kemmerer's empirical and theoretical work focuses mainly on how different conceptual domains are mediated by different cortical systems. He is especially interested in the relationships between semantics, grammar, perception, and action, and in cross-linguistic similarities and differences in conceptual representation. He has published over 60 articles and chapters, and also wrote an introductory textbook called *Cognitive Neuroscience of Language 2015*.

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CHAPTER 1

NEUROLINGUISTICS

A Brief Historical Perspective

SHEILA E. BLUMSTEIN

THE past 50 years have witnessed a revolution in our understanding of how the faculties of mind intersect with the brain. A major piece of this endeavor is neurolinguistics, the study of the neural mechanisms underlying language. The scientific field of neurolinguistics was originally defined by Harry Whitaker and remains the centerpiece of the journal *Brain and Language*, which he founded in 1974. However, the spirit of neurolinguistics predates the 1970s and has been and continues to be the subject of study under the guise of a number of other disciplines, including neuropsychology, aphasiology, psycholinguistics, and the cognitive neuroscience of language. While it is beyond the scope of this chapter to chart the complete history of the study of the brain and language, it will provide a retrospective view, focusing on the foundations from which our current knowledge and questions derive, the theoretical underpinnings that still guide much of our current research, what we have learned, and what questions and challenges remain for the future.

NEUROPSYCHOLOGY OF LANGUAGE AND THE BIRTH OF NEUROLINGUISTICS

There is a long history examining the effects of brain injury on language. From the work of Paul Broca and Carl Wernicke, it was shown that lesions to particular areas of the brain had specific and different consequences on language behavior. Indeed, classical aphasiology, exemplified by the works of Kurt Goldstein (1948), Henry Head (1926), and Alexander Luria (1966), to name a few, provided detailed descriptions of the clinical syndromes that emerged pursuant to lesions to particular areas of the brain. These clinical syndromes identified a constellation of impaired and spared language abilities centering on the following: speech output, its fluency and articulation; auditory comprehension of sounds, words, sentences; naming; repetition of words and sentences; and secondary language skills including reading and writing. Among these syndromes, it is the language behavior of patients who were clinically classified as Broca's, Conduction, and Wernicke's aphasia that served as the primary foundation for the detailed examination of the nature of the underlying language deficits.

From this work emerged the view that language for most individuals was left-hemisphere dominant, and that there was a direct relation between neural areas and language function (i.e., one could "predict" the aphasia syndrome based on lesion site and vice versa). Indeed, the seminal monograph *Disconnexion Syndromes in Animals and Man*, written by Norman Geschwind (1965), built on the classical work of the nineteenth- and twentieth-century "diagram makers." The diagram makers, led by Wernicke and Ludwig Lichtheim, identified brain regions that were "centers" specialized for particular language functions, and they mapped out, in the form of diagrams, these centers and the connections between them. In this view, damage to these functional centers or to the connections between them gave rise to the classical aphasia syndromes (for a detailed review, see Levelt, 2013). Lesion localization was limited by the technology of the day, and, as we will see, with increased advances, the accuracy of lesion-symptom mapping could not be sustained in its entirety. Nonetheless, the notion that there were functionally specialized neural centers with white and gray matter connections between them was a major advancement in the field, as it became the working model characterizing language deficits in aphasia and language-brain relations more broadly.

While the aphasia syndromes provided a rich tapestry of spared and impaired language abilities, they beg the question of what aspects of linguistic function may be compromised. In particular, linguists have long assumed that language is broken down into a hierarchy of structural components, including sounds (phonetics and phonology), words (the lexicon), sentences (syntax), and meaning (semantics). Each of these components has its own set of properties or representations.

Considering language deficits in aphasia from this linguistic perspective, a different set of questions arise, one that more directly addresses the nature of language deficits in aphasia. Here, for example, one can ask whether the basis of the auditory comprehension deficit in Wernicke's aphasia is due to an impairment in processing the sounds of speech, in mapping sounds to words, in processing the meanings of words, or whether the nonfluent, often agrammatic production deficit of Broca's aphasics is due to an articulatory/phonological impairment, a syntactic impairment, or simply to an economy of effort. And more generally, one can ask whether linguistic deficits in aphasia reflect impairments to representations or to the processes that access them. This is not to say that there was no attempt by the early aphasiologists to "explain" the nature of the deficits giving rise to aphasia. For example, Broca proposed that the third frontal convolution (i.e., Broca's area) was the "center for articulated speech" and Wernicke proposed that the auditory comprehension impairment of Wernicke's aphasics was due to a deficit in "auditory images." However, what distinguished these classical approaches to the syndromes of aphasia and the more modern era was that the functional centers were defined descriptively absent a linguistic theoretical framework, and the hypothesized functions were based on clinical observations rather than being tested experimentally.

The beginning of the modern era in neurolinguistics began with linguistic approaches to aphasia. There were two pioneers, Roman Jakobson and Harold Goodglass, who most clearly led this new approach to the study of the brain and language. Roman Jakobson was perhaps the first linguist to consider the aphasias from a linguistic perspective, suggesting that the breakdown of speech in aphasia and its development in children reflect phonological universals of language (Jakobson, 1941, translated 1972), and proposing that the output deficits in Broca's and Wernicke's aphasia reflect impairments in syntagmatic and paradigmatic axes of language, with a syntagmatic deficit giving rise to Broca's aphasics' syntactic deficit and a paradigmatic deficit giving rise to Wernicke's aphasics' paragrammatic deficit (Jakobson, 1956). Interestingly, in present-day parlance, this distinction reflects a sequencing disorder for Broca's aphasics and a word selection disorder for Wernicke's aphasics. Harold Goodglass, who established the Boston Aphasia Research Center along with the neurologist Norman Geschwind and led it from the mid-1960s to 1996, was among the first to apply experimental methods drawn from psycholinguistics and cognitive psychology to systematically examine the nature of linguistic deficits in aphasia (Goodglass, 1993). It is this multidisciplinary approach, focusing on the confluence of the study of the classical aphasia syndromes with theoretical approaches to language and experimental methodology, that gave birth to what we now call *neurolinguistics*.

Experimental Approaches to the Study of Language Deficits in Aphasia

Neurolinguistic approaches to the study of aphasia were guided by the view that language is hierarchically organized into structural components and that these structural components mapped directly to functionally defined neural regions. Thus, the focus was on conducting parametric studies of linguistic features of the classical aphasias. For Broca's aphasics, the emphasis was on potential syntactic impairments and phonetic/phonological deficits. Early results suggested that indeed Broca's aphasics not only had agrammatic deficits in production, but also displayed auditory comprehension impairments when the only cues available were syntactic in nature (Zurif & Caramazza, 1976; Zurif, Caramazza, & Myerson, 1972). Moreover, studies of the acoustic properties of speech production suggested that these patients had articulatory/phonetic planning impairments (see Blumstein, 1981, for review). For Wernicke's aphasics, the question was whether their auditory comprehension impairments were due to phonological deficits where phonemic misperceptions might give rise to selecting incorrect words (e.g., hearing *bear* and pointing to *pear*) or were due to semantic impairments reflecting deficits in the underlying meaning representations of words or in accessing the meaning of words. Early results suggested that although these patients do have deficits in perceiving phonological contrasts, it did not predict the severity of their auditory comprehension impairments (Basso, Casati, & Vignolo, 1977; Blumstein, Baker, & Goodglass, 1977; but see the following section, "The Modern Era," in this chapter). Those studies examining word meaning indicated that the underlying representations of words appeared to be relatively spared in aphasia, while access to meaning and the time course of mapping sounds to word meanings was impaired (Milberg & Blumstein, 1981; Swinney, Zurif, & Nicol, 1989; but see the following section, "The Modern Era," in this chapter). A broad range of behavioral paradigms have been used in these studies, including discrimination, identification, and psychophysical experiments of speech, word and/or picture matching, lexical decision, hierarchical clustering, and grammaticality judgments, to name a few.

Nonetheless, this approach using aphasia syndromes as a basis for neurolinguistic investigations was not without its critics. They came from two directions. One reflected a challenge to group studies using the classical aphasia syndromes, and the other reflected a challenge to one-to-one mapping between aphasia syndrome and lesion localization. With regard to the former, it was proposed that clinical syndromes do not necessarily cut across linguistic domains, and hence the study of patients grouped by aphasia syndrome may not provide a window into the particular linguistic deficit (Caramazza, 1984, 1986). Moreover, classification is a "messy" thing; there is variability in severity across patients within the defining properties of the syndrome, and some patients do not have all of the symptoms included in the classification schema. Hence, in this view, group studies using the classical aphasia syndromes are by their very nature fundamentally flawed (Schwartz, 1984).

To mitigate this concern, these researchers took a single case study approach where detailed analyses were conducted of particular linguistic deficits. The overarching goal was to use the effects of brain damage as a window into current linguistic theories and theories of language processing (Caramazza, 1986). However, in contrast to classical neuropsychological case studies that described unique behavioral patterns in relation to lesion localization, this approach was typically agnostic with respect to the lesion status of the patient. Hence, while it provided interesting insights into the linguistic nature of deficits in aphasia (see Rapp & Goldrick, 2006, for a review), this case study approach did not consider the neural systems underlying such deficits, and hence provided limited insight into the relation between brain and language.

Turning to lesion localization of the aphasia syndromes, technological advances in neuroimaging over the past 20 years have provided a cautionary tale for the view that there is a one-to-one mapping between aphasia syndrome and lesion. First, the lesions associated with the classical aphasias were typically described incorrectly as only cortical. However, in fact, lesions of patients commonly include both cortical and subcortical structures (see Copland & Angwin, Chapter 33 in this volume). Second, lesions of patients with aphasia are rarely focal; rather, they tend to be large, encompassing a number of neural regions. If the lesions are focal, patients typically present with transient aphasias, not the chronic syndrome profile of the classical aphasias. Third, there is variability across lesion profiles. As one might expect, no aphasic has exactly the same lesion profile. As a result, there are differences across aphasics in the degree of damage in a particular area, as well as in the extent to which a lesion extends to other areas of the brain. Finally, research has shown that there is not a one-to-one relation between aphasia syndrome and lesion localization. For example, not all Broca's aphasics have lesions in Broca's area (BA45), nor do all patients with damage in Broca's area present with Broca's aphasia (see Dronkers, 2000).

These issues notwithstanding, neurolinguistic investigations using the aphasia syndromes have provided the basis for much of the modern era spanning the last 20 years. The aphasia syndromes have provided a theoretical framework for examining linguistic deficits, suggesting that the temporal lobe is involved in accessing the meanings of words, that the superior temporal gyrus is involved in auditory processing of speech, that posterior temporal areas are involved in integrating auditory and articulatory processes, and that the inferior frontal gyrus (IFG) is involved in processing syntax and articulatory planning as well as in selection processes for words. Critically, these studies have shown, across patient groups and lesion sites, similar patterns of performance as a function of linguistic structural complexity. For example, for all patients, structurally more complex sentences are more difficult to comprehend and also to produce, and the perception and production of phonologically similar words result in increased errors compared to words that share few phonological attributes. Despite claims that deficits are "selective" to a particular component of the grammar (e.g., syntax), nearly all aphasics, regardless of syndrome, display impairments that affect multiple linguistic components of language, although the severity of the impairment and the underlying functional impairment may differ.

Taken together, these studies were among the first to suggest that neural systems underlying different components of the grammar are broadly tuned, recruiting neural systems rather than functionally encapsulated neural regions (see the following section, "The Modern Era," for further discussion). Nonetheless, although patients across syndromes may appear to share a common impairment to a particular aspect of language, the patterns of performance of the patients may differ, suggesting that different functional impairments emerge as a function of lesion site. For example, both Broca's and Wernicke's aphasics show lexical processing impairments. However, examining access to words that share phonological attributes and hence are lexical competitors (e.g. hammer vs. hammock), lexical candidates appear to stay active longer than normal for Wernicke's aphasics. In contrast, Broca's aphasics fail to select the target from among competing lexical alternatives (Janse, 2006; Utman, Blumstein, & Sullivan, 2001; Yee, Blumstein, & Sedivy, 2008). These findings support the structural integrity of the lexical system in these two groups of patients since lexical access is influenced by whether lexical items are competitors or not, but suggest different processing impairments in each group, presumably reflecting the distinct functional roles of temporal and frontal lobe structures in lexical access.

The Modern Era

It is difficult to demarcate when the “modern era” began, as science typically progresses incrementally. Nonetheless, there are a number of factors that contributed to what characterizes today’s approach to neurolinguistics. One has to do with the increased influence of computational models that focus on the nature of information flow in the language system (cf. Dell, 1986; Marslen-Wilson, 1987; McClelland, 1988). These models enriched earlier structural models in which components of the grammar were separate, encapsulated modules (cf. Fodor, 1983). Additionally, computational models have been used to characterize language impairments in aphasia in terms of processing deficits (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; McNellis & Blumstein, 2001; Mirman, Yee, Blumstein, & Magnuson, 2011; Rapp & Goldrick, 2000).

Neurobiologically inspired computational models, beginning with the Parallel Distributed Processing (PDP) models of the 1980s (Rumelhart & McClelland, 1986) and continuing through contemporary models (Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015; Horwitz, Friston, & Taylor, 2000; Wennekers, Garagnani, & Pulvermuller, 2006), are a major advance as they seek to develop neurally plausible models of how the brain processes speech and language. For example, the use of neuron-like elements allow for graded responses to stimulus input, and Hebbian learning mechanisms can characterize word learning (Garagnani, Wennekers, & Pulvermuller, 2007). Hebbian learning has also been used to simulate lexically guided tuning effects on speech perception (Mirman, McClelland, & Holt, 2006).

Without question, the single most important factor that has influenced the current state of the art in neurolinguistics research is technological advances that have revolutionized our ability to map structural and functional properties of the brain. It is beyond the scope of this introductory chapter to review all of the methods, the advantages and disadvantages of each, and their contributions to our understanding of the neural basis of language, but suffice to say they provide a broad spectrum of tools that afford different sources of information about neural activity. To briefly consider a few, functional magnetic resonance imaging (fMRI) has had perhaps the greatest influence because it is a noninvasive procedure that allows for examining neural activation patterns with parametric manipulations of linguistic constructs (see Heim & Specht, Chapter 4 in this volume). Other important methods that are now a part of the toolbox of the neurolinguist include transcranial magnetic stimulation (TMS) that allows for the creation of “virtual lesions” (see Schuhmann, Chapter 5 in this volume), and electrophysiological measures such as event-related potentials (ERPs; see Leckey & Federmeier, Chapter 3 in this volume) and magnetoencephalography (MEG; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume) that provide crucial information about the time course (in ms) of processing. Enhanced structural information comes from magnetic resonance imaging (MRI), which has provided advances in understanding the structural properties of the normal brain and in mapping lesions using voxel-based lesion mapping (Bates, Wilson, Saygin, Dick, Sereno, Knight, & Dronkers, 2003; see Wilson, Chapter 2 in this volume). Additional insights come from diffusion tensor imaging (DTI), which measures white matter fiber tracts and connections between different parts of the brain (see Catani & Forkel, Chapter 9 in this volume).

These technological advances have enriched and deepened the ability to study the neural processing of language and have opened up new avenues of research, including examining neural systems underlying language processing in the normal brain, comparing the relation between language processing in the normal brain with that of the diseased brain, charting potential changes in the neural systems underlying language across the life span, and investigating the plasticity of the neural system in persons under conditions of natural recovery or as a result of rehabilitation techniques. These research areas are by no means all inclusive, but they underscore how technological advances can open up new and critically important avenues of research that hold the promise of providing deeper insights into our understanding of language and the brain. Let us consider a few of these as a window into the neurolinguistics of today.

There is a vast literature that has examined the neural substrates of language using fMRI. Among the many contributions of functional neuroimaging studies, there are two sets of findings that have challenged earlier theoretical assumptions. The first concerns the extent to which the organization of language is strictly modular, with components of the grammar having a distinct neural locus, and the second concerns the nature of information flow between and among components of the grammar.

Turning to the modularity of components of language, fMRI studies investigating the neural areas involved in processing different components of the grammar have shown that the neural substrates of phonetics/phonology, the lexicon, syntax, and meaning do not recruit a single neural area dedicated to its processing, but rather each recruits a broadly distributed network or processing stream (for reviews, see Binder, Desai, Graves, & Conant, 2009; Hickok, 2009; Hickok & Poeppel, 2007; Kaan & Swaab, 2002; Blumstein & Myers, 2013; Price, 2012). Thus, the brain is not divided into functionally dedicated "linguistic" modules. For example, although the superior temporal gyrus and superior temporal sulcus appear to be recruited in the early auditory processing of the speech signal, neural activation occurs in other areas, including the middle temporal gyrus (MTG), parietal areas including the angular gyrus (AG) and supramarginal gyrus (SMG), and frontal areas including the IFG (e.g., Hickok & Poeppel, 2007; Scott & Wise, 2004). Although they appear to have different functional properties, these neural areas work together as part of a single system involved in the perception of speech. Similar findings have emerged in examining neural activation patterns of the lexicon, syntax, and semantics (Vigneau, Beaucousin, Herve, Duffau, et al., 2006). Interestingly, precursors to these fMRI findings are found in the behavioral studies of the aphasia syndromes. Here, Broca's and Wernicke's aphasics display impairments in multiple components of the grammar, including speech, lexical, syntactic, and semantic processing, although the severity and the functional basis of the deficit appear to differ across these groups (Blumstein, 1995).

The fMRI findings have also shown that information flow between components of the grammar is interactive such that activation in one component of the grammar directly influences activation in other components of the grammar. Thus, for example, the lexical structure of words has a modulatory effect not only on neural areas involved in lexical access (SMG), but also in areas involved in phonological and phonetic processing (IFG and pre-central gyrus) (Peramunage, Blumstein, Myers, Goldrick, & Baese-Berk, 2011). Such evidence is consistent with cascading models of language processing in which information at one level of processing influences processing downstream from it. Such findings challenge those models in which processing within one component of the grammar is separate from and independent of processing in other components (e.g., Levelt, Roelofs, & Meyer, 1999).

An important, relatively new direction that the field has taken is to examine the neural systems underlying language using more than one neuroimaging and/or electrophysiological method. As indicated earlier, the lesion method has limitations because lesions tend to be very large, making it difficult to assess what neural areas contribute to, or are "responsible" for, the particular language impairment. Related issues arise from fMRI studies (see Heim & Specht, Chapter 4 in this volume). Typically, multiple neural areas show activation, and researchers infer the functional role of these areas, often drawing from current models of the neural architecture of language. Thus, it is not clear what actual role these areas may play, or if they are even involved in the linguistic "function" under investigation (Price, Mummery, Moore, Frackowiak, & Friston, 1999; Rorden & Karnath, 2004). Moreover, areas other than the classical language areas may be activated. However, it is not known what role, if any, these play in language processing. Two methods have provided a critically important window into this potential challenge. The first is to couple fMRI results with MRI analyses of lesion data, and the second is to couple fMRI with TMS. In both cases, it would be expected that either a real or "virtual" lesion to a particular neural region that was activated under normal conditions using fMRI would result in a behavioral deficit or a decrement in processing.

Finally, the modern era has witnessed a renewed interest in localization using voxel-based lesion mapping to examine the effects of brain injury on language processing (Bates, Wilson, Saygin, Dick, Sereno, Knight, & Dronkers, 2003; see Wilson, Chapter 2 in this volume). With greater precision in quantitatively identifying and measuring the location, size, and extent of lesions, new results extend and clarify past findings. In particular, in contrast to earlier findings, it has been shown that phonological perception impairments predict auditory language comprehension deficits in Wernicke's aphasics, although these patients may also display deficits in accessing word meaning (Robson, Keidel, Lambon Ralph, & Sage, 2012). Furthermore, contrary to the view that the lexical-semantic network is preserved in aphasia, degradation of semantic structure does occur in aphasic patients with lesions extending to the anterior temporal lobe (Jeffries & Lambon Ralph, 2006; Walker, Schwartz, Kimberg, Faseyitan, et al., 2011).

Neurolinguistics in the modern era has also begun to play a central role in the adjudication and development of a number of competing theories of language. Here, the notion is that activation of particular neural areas will distinguish between/among the claims made by these theories. For example, there are current opposing views as to whether lexical representations are "embodied" or symbolic (amodal) (for reviews, see Jirak, Menz, Buccino, Borghi, & Binkofski, 2010; Kiefer & Pulvermuller, 2012). If embodied, reflecting our experience with words and the sensorimotor systems that are activated in the use of these words, then there should be activation in the particular sensorimotor system that is represented in that concept when hearing or using a word (for example, to "pick up" a paper requires hand motor activity, whereas to "kick" a ball requires foot motor activity; see Pulvermüller, Shtyrov, & Ilmoniemi, 2005). If symbolic, there would not be a systematic relation between a word's meaning and activation of the sensorimotor systems it relates to, and amodal neural areas would be activated.

There are a number of other questions raised by competing theories that are currently being "tested" using neuroimaging techniques. These include the following:

- Are speech perception representations motor (articulatorily or gesturally based) consistent with claims of the motor theory of speech perception (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967; for neural evidence, see Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Wilson, Saygin, Sereno, & Iacoboni, 2004), or acoustic (auditorily based) consistent with early distinctive feature theories and the acoustic theory of speech perception (Jakobson, Fant, & Halle, 1961; Stevens & Blumstein, 1981; for neural evidence, see Chang, Rieger, Johnson, et al., 2010; Cheung, Hamilton, Johnson, & Chang, 2016; Lotto, Hickok, & Holt, 2009)?
- Is the influence of contextual factors on degraded speech perceptual (Marslen-Wilson & Tyler, 1980) or post-perceptual (Norris, McQueen, & Cutler, 2000)?
- Is language modular (Federenko & Thomspon-Schill, 2014), or is it built on domain general functions, processes, and/or computations (Blumstein & Amso, 2013; Kelly & Martin, 1994)?

While the jury is still out, and the debates continue, further evidence from neurolinguistics using state-of-the-art imaging and analysis techniques holds the promise of not only distinguishing among the claims made by these theories, but potentially developing new and unique theories.

Future Directions and Challenges

While it is clear that the processing of language recruits a broad network of areas, the functional role of these areas needs to be more clearly delineated, as typically the functional role of these regions is inferred, based on traditional models of the neural organization of language. A focus on networks examining functional and/or effective connectivity (Friston, 1994; Horwitz, Friston, & Taylor, 2000), rather than individual neural regions, is a critical next step for understanding the complexities of language processing. Moreover, while it is clear that components of the grammar activate a neural processing stream, the direction of information flow has not been fully mapped out (for overviews of grammatical processing, see, in this volume, Kemmerer, Chapter 30; Thompson & Mack, Chapter 31). Indeed, as described earlier, there is an ongoing debate in the literature about the extent to which information flow is bottom-up, with contextual influences on sensory processes reflecting executive decision-related processes, or whether information flow is also top-down, with higher-level information sources influencing lower levels of sensory processing (Guediche, Blumstein, Fiez, & Holt, 2013). Here, functional connectivity analyses and methods sensitive to the time course of processing, such as MEG and ERP, coupled with the good spatial resolution afforded by fMRI, hold the promise of providing useful insights. Further questions along these lines are to understand how linguistic information across modalities is integrated. How do production (articulatory) processes influence perception (auditory) processes (see, in this volume, Hickok, Chapter 20; Poeppel, Cogan, Davidesco, & Flinker, Chapter 26)? How does visual information in speech production integrate with auditory information in speech perception? (see, in this volume, Newman, Chapter 14; Corina & Lawyer, Chapter 16; Rapp & Purcell, Chapter 17)? How does literacy (reading) affect the neural organization of language (access to speech, words, meaning) (see, in this volume, Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24; Jasinska & Landi, Chapter 25)?

A yet unanswered question is what role the right hemisphere plays in linguistic processing. Contradictory information comes from fMRI and lesion studies. In particular, fMRI studies commonly show activation not only in the left hemisphere, but also in homologous areas of the right hemisphere during linguistic tasks. And yet, patients with right hemisphere lesions do not typically display linguistic deficits (although they do show impairments in the pragmatics of language and discourse processing). Current findings using fMRI to examine neural changes during recovery in aphasia suggest that initially aphasics with unilateral left hemisphere lesions show increased activation of right hemisphere structures. However, those who recover the best show progressively less right hemisphere activation with increased activation in perilesional areas of the left hemisphere (Pizzamiglio, Galati, & Committeri, 2001). How then can fMRI findings be reconciled with lesion results to determine the role of the right hemisphere in linguistic processing (see Van der Haegen & Cai, Chapter 34 in this volume)?

Finally, a major challenge for the field is to resolve what appear to be contradictory claims about the functional role of certain neural areas, as different linguistic and/or cognitive "functions" have been attributed to the same neural areas. For example, the IFG has been implicated in speech production and perception (Hickok & Poeppel, 2007; Price, 2012), phonetic categorization (Myers, Blumstein, Walsh, & Eliassen, 2009), syntactic processing (Grodzinsky & Friederici, 2006), semantic processing (Binder, Desai, Graves, & Conant, 2009), and executive decision-making (Badre & Wagner, 2007; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Similarly, the superior temporal sulcus has been implicated in speech perception and in a broad range of cognitive domains, including face processing, biological motion, social perception, theory of mind, and audiovisual integration (Hein & Knight, 2008).

One yet unanswered question is whether the field of neurolinguistics will ultimately lead the way to the development of new models and theories of language processing. The intersection of mind (language) and brain is uniquely the purview of neurolinguistics, and understanding brain organization, function, and processes provides constraints on models and theories of language. Here, there is room for cautious optimism. If, for example, evidence shows that language is built on more general domain computations, then it may provide the impetus to develop new models of language processing that do not rely on "specialized" vocabularies or representations at each level of the grammar.

Neurobiologically plausible computational models will undoubtedly play an even greater role than they do currently. As described earlier, such efforts have already begun. However, to provide new insights into the neural basis of language, these models will also need to reflect the complexities inherent in language processing. That is, they will need to be able to not only reflect the functional architecture inherent within a linguistic level (e.g., the phonological and statistical properties giving rise to lexical density), but also model how such information affects processing throughout the system. Further, such models will also need to consider how new words are added throughout the life span without destabilizing the network. For example, they will need to differentiate a production of a word that is idiosyncratic (i.e., produced in a nonstandard way by a speaker) from one that is a new entry, and they will have to allow for creating a new representation of a word as it is being introduced into the lexicon. At early stages, its frequency of occurrence would be greater than zero but still of a very low frequency, and thus the word would be potentially incorrectly classified as a nonword. Finally, computational models will need to be able to scale up, including a large number of stimuli and a broad range of linguistic parameters that not only respect the functional architecture of the language system, but also cut across levels of linguistic processing.

One area where contributions from neurolinguistics may be unique and critically important is in the area of language rehabilitation. Basic understanding of the theoretical foundations of language and its neural instantiation provides a critical bridge to rehabilitation. As we understand the functional role that particular areas play within the neural system, targeted rehabilitation treatments may be developed that more likely tap the underlying deficit. That is, rather than treating a particular language impairment in aphasia as a unitary deficit across patients who have varying lesion profiles and symptom complexes, different rehabilitation programs should be developed that reflect the functional role of the neural areas that are lesioned. Thus, as described earlier, although damage to either temporal or frontal structures results in deficits in lexical selection, damage to temporal structures appears to result in a failure to inhibit lexical competitors, whereas damage to frontal structures appears to result in an inability to select among competing alternatives. Although both types of aphasics then display lexical access impairments, the deficits are not the same, and the nature of therapy developed for these patients should presumably differ.

Additionally, as it becomes clearer that language shares more general processes with other cognitive domains, rehabilitation programs can apply general cognitive principles to language rehabilitation strategies. Some recent results suggest that such approaches have potential to enhance language recovery. For example, variability of linguistic input is the norm in real-world environments and appears to enhance language communication. Experimental studies and rehabilitation programs, however, typically remove such variability; they present stimuli controlling for variability in order to home in on the particular linguistic parameter being targeted for rehab. There are some hints in the literature that aphasic participants' performance is facilitated when presented with stimuli that are not typical or that may vary from the norm. As an example, Kiran and Thompson (2003) showed that exposure to atypical exemplars of words in a semantic category generalized to naming of both atypical and typical members of the category in aphasic participants; exposure to typical members did not generalize to atypical members or other members of the category.

Finally, theoretical approaches to language generally consider it to be static—never changing either within the environment, within the individual, or across the life span. We know that this is not correct. Language is processed under multiple conditions of variability—the environment is noisy, there is variability in speech production of individuals as well as in their perceptual "acumen," and there are changes in language processing over time. Yet, both speakers and listeners maintain stability in processing under such "adverse" conditions. We know little about how the neural system accommodates these multiple sources of variability, and what conditions give rise to changes to the neural substrate in development, aging, or pursuant to brain injury. Ultimately, theories of language will have to account for such variation, and neurolinguistics is positioned to provide the foundation for the development of these new models.

In summary, the history of research in neurolinguistics has provided an evolving picture of the neural basis of language. We have witnessed how the field has progressed from a singular focus on the aphasias to the application of a broader palette of methodologies. These methods, in conjunction with the lesion method, have enriched and revolutionized our understanding of language and its neural basis and have provided both new insights and new challenges. No doubt new technological advances will be developed in the next decade, as will richer computational models of language processing. Together, they will enhance neurolinguistics, leading us to a deeper understanding of language—its representations, organization, and processes—and the neural systems underlying it—their structure, connections, computations, and intersection with other cognitive domains.

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PART I

THE METHODS

CHAPTER 2

NEUROLINGUISTIC STUDIES OF PATIENTS WITH ACQUIRED APHASIAS

STEPHEN M. WILSON

Introduction

Our earliest insights into the neural underpinnings of language came from studies of patients with acquired aphasia, that is, deficits in producing and/or comprehending language, due to brain damage. Descriptions of aphasia can be found in the medical literature dating back to about 400 b.c.e. (Benton & Joynt, 1960), and there is even a possible reference to aphasia with right hemiplegia in the Bible, dating back to a similar time: "If I forget you, Jerusalem, may my right hand forget its skill. May my tongue cling to the roof of my mouth if I do not remember you" (Psalm 137:5–6, New International Version). The association of aphasia with a motor deficit in the right hand could conceivably reflect an understanding that language is localized to the left hemisphere (Benton, 1971). In the early nineteenth century, physicians of the phrenological school, including Gall, Spurzheim, and Bouillaud, postulated that language was a function of the frontal lobes, based in part on observations of patients with frontal lobe damage and deficits in speaking (Bouillaud, 1825; Gall, 1825; Spurzheim, 1815). In 1836, Marc Dax, a French neurologist, even prepared a paper in which he observed an association between aphasia and damage to the left hemisphere (Dax, 1836/1865); however, there is no evidence that the paper was actually presented at the conference for which it was prepared (Levelt, 2013).

The modern field of neurolinguistics began in earnest with a series of papers by Paul Broca in the first half of the 1860s. Broca's first paper was a case report of a patient who could not produce spoken language, and who came to autopsy just a few days after Broca examined him (Broca, 1861). Broca found that although the patient's brain was damaged quite extensively, the epicenter of the damage appeared to be the inferior frontal gyrus of the left frontal lobe, leading him to hypothesize that this brain region is responsible for our ability to speak aloud. Broca's claim generated great interest, and before long, numerous similar cases had been described. A few years after his first case, Broca observed the striking fact that virtually all reported cases of aphasia involved damage to the left hemisphere, almost all involved concomitant paralysis of the right hand, and aphasia rarely occurred after damage to the right hemisphere. From these observations, he concluded that language must be localized in the left hemisphere (Broca, 1865).

Ten years later, Carl Wernicke, a young German physician, reported two patients with damage to the posterior superior temporal lobe and deficits in language comprehension (Wernicke, 1874), suggesting for the first time that there was not a single language area, but multiple language areas with distinct functions. Wernicke developed an extraordinarily prescient theory of the neural organization of language. Ludwig Lichtheim, a German neurologist, refined and expanded on Wernicke's model (Lichtheim, 1885), laying a firm foundation for the field of neurolinguistics as we know it today (Caplan, 1987; Levelt, 2013).

Three main approaches to patient studies can be identified in the literature. In the first, which we will call the *cognitive neuropsychological approach*, researchers undertake comprehensive investigations of single patients in order to document patterns of impaired and spared functions in one or more components of the language system, and make inferences about the normal functional architecture of the language system. In the second approach, which we call the *syndromic approach*, researchers study groups of patients defined by sharing a clinical syndrome (e.g., Broca's aphasia) or a clinical feature (e.g., agrammatism), in order to characterize the precise nature of linguistic deficits, co-occurrence of symptoms, patterns of recovery, and so on. The third approach we will call the *lesion-deficit correlation approach*. Here, researchers investigate the relationships between damage to different brain regions and different kinds of language deficits, so as to uncover the functional neuroanatomy of the language system. Some studies blend aspects of more than one of these three approaches. All three approaches assume that language functions as a modular system, the components of which can be damaged independently of one another. The rich body of literature that has followed from this fundamental assumption is evidence of its basic soundness. The lesion-deficit approach further assumes that the functionally modular components of the language system are to some extent physically localized in specific brain regions or networks, usually but not always taken to be relatively consistent across individuals.

We will discuss these three approaches by focusing on representative studies that exemplify their strengths and weaknesses. But first, we need to consider the individuals with acquired aphasias from whom we hope to learn something about the neural basis of language. Who are they? What kinds of brain damage lead to acquired aphasia? Does it matter how the damage came about?

Patients with Acquired Aphasias

There are numerous ways that language regions of the brain can become damaged, such as stroke, neurodegenerative disease, neurosurgical resections, or trauma. In general, damage to brain regions involved in language processing can be expected to result in similar deficits regardless of how the damage came about. However, there are important differences between patients with acquired aphasias due to different etiologies, such as typical distributions of damage, the time course of damage and/or recovery, and whether damage is complete or gradated.

The single most common cause of acquired aphasia is stroke. There are two reasons for this. First, strokes are very common. Approximately 800,000 people in the United States experience a stroke each year; rates are similar in other economically developed countries, and even higher in less economically developed countries. Second, the incidence of aphasia is very high after stroke due to the anatomy of the vasculature, which dictates which brain regions are typically damaged. The most common type of stroke is ischemic stroke, which occurs when arteries supplying the brain are blocked by blood clots. The reduction or cessation of blood flow causes infarction (cell death) in the region(s) supplied by the artery. A large artery named the middle cerebral artery runs through the Sylvian fissure, giving off branches that supply the majority of the lateral cerebral hemispheres. Key language regions, including Broca's area and Wernicke's area, are located in the immediate vicinity of the Sylvian fissure, so blockages of different branches of the middle cerebral artery can readily cause damage that is localized to specific language regions. Moreover, blockage in the trunk of the middle cerebral artery can cause damage to multiple language regions.

While ischemic strokes in the left middle cerebral artery almost invariably cause aphasia, other types of strokes can also lead to aphasia. Two other arteries supply the remainder of the cerebral hemispheres: the posterior cerebral artery and the anterior cerebral artery. Ischemic strokes in either of these arteries, but especially the posterior cerebral artery, often result in aphasia. Brain regions at the peripheries of vascular territories are susceptible to global reductions in blood flow, usually from a blockage in the neck. These so-called watershed strokes often affect frontal or parietal regions and often result in aphasia. Finally, in addition to ischemic strokes, which make up about 85% of strokes, there are also hemorrhagic strokes, which involve leakage or rupture of a blood vessel in the brain, causing cell damage or cell death. Hemorrhagic strokes have a different distribution of affected areas than ischemic strokes, but common sites include the basal ganglia, the thalamus, and the cerebral hemispheres, damage to all of which can potentially lead to aphasia. While many of the regions that are often impacted by stroke appear to be involved in language function, the regions damaged by stroke are by no means evenly distributed: regions adjacent to the middle cerebral artery, such as the insula, are very frequently damaged, whereas other regions such as the anterior temporal lobes are rarely damaged, and practically never damaged in isolation.

The onset of language deficits after a stroke is usually sudden, or at least rapid (over the course of hours). However, language deficits are by no means static. Rather, almost all patients with aphasia experience some degree of recovery of language function after a stroke. The greatest gains are often made in the first day or two, and largely reflect the resolution of blood flow deficits in penumbral regions beyond the irreversibly damaged region (Hillis et al., 2002). After this initial period, much less is known regarding the mechanisms underlying recovery, which may include resolution of edema, continued perfusion changes, and neuroplasticity (Heiss, Karbe, et al., 1997; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Saur et al., 2006; Saur & Hartwigsen, 2012). While the greatest gains take place within the first three months (Kertesz & McCabe, 1977; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1995), many patients continue to improve substantially after that time period (Naeser et al., 1998; Smania et al., 2010; Swinburn, Porter, & Howard, 2004).

In sum, patients who survive strokes provide a rich source of data on the neural basis of language, due to the high incidence of stroke, the high incidence of aphasia after stroke, and the anatomy of the middle cerebral artery with respect to key language regions. Major challenges of studying stroke patients include the uneven distribution of lesion locations, which is dictated by the vascular anatomy, and the substantial recovery that typically takes place relatively rapidly, such that most studies are carried out after significant functional reorganization has probably already taken place.

A second relatively common cause of aphasia is neurodegenerative disease. There are many different neurodegenerative diseases, which impact different brain regions, and progress in different ways. When language regions of the brain are affected before other regions, then language deficits will be the first symptoms of the disease. This is termed *primary progressive aphasia* (PPA) (Mesulam, 1982, 2001). Mesulam (2001) defines PPA as a slow, insidious onset and gradual progression of speech and/or language deficits, with no other significant deficits (e.g., memory problems, apathy, disinhibition) for at least two years, and with language remaining the most impaired function when other deficits do emerge.

Language deficits can be remarkably focal early in the course of the disease. Recent consensus guidelines for the diagnosis of PPA recognize three variants: nonfluent/agrammatic PPA; semantic PPA (also known as semantic dementia); and logopenic PPA (Gorno-Tempini et al., 2011). The three variants have different underlying pathological causes (Grossman, 2010; Snowden et al., 2011), different distributions of atrophy (Gorno-Tempini et al., 2004), and following from that, differential impacts on various speech and language domains (Wilson, Henry, et al., 2010).

There are three important differences in the nature of brain damage between PPA and stroke. First, whereas strokes typically completely destroy any affected brain regions, in PPA the damage is graded, not absolute. Atrophy begins gradually and progresses over time. Affected regions still contain neural tissue, and the extent to which it retains its functionality is an empirical question, which can be addressed with methodologies such as functional magnetic resonance imaging (fMRI) (Wilson, Dronkers, et al., 2010).

Second, neurodegenerative diseases tend to impact functional networks of regions, which may or may not be spatially contiguous (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). For instance, semantic dementia impacts anterior and ventral temporal regions bilaterally, even though the left and right temporal regions that are affected in each hemisphere are not adjacent. Degeneration of functionally connected networks may result in more discrete linguistic deficits than damage to regions that happen to be spatially adjacent, but which may or may not have anything in common functionally.

Third, the regions that are impacted in PPA are not the same as those typically damaged in stroke. Most important, the anterior temporal lobes are rarely damaged in isolation in stroke, due to vascular anatomy (Holland & Lambon Ralph, 2010), whereas they are damaged in quite a focal manner in semantic dementia (Hodges, Patterson, Oxbury, & Funnell, 1992). Another example is that it is relatively common in PPA to find patients with significantly disproportionate damage to dorsal or ventral white matter tracts connecting frontal and temporal language areas (Wilson, Galantucci, et al., 2011). This contrasts with the situation in stroke, in which middle cerebrary artery strokes are more likely to damage either both tracts or neither tract, making their functions hard to dissociate (Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013).

In sum, then, some of the advantages to the study of PPA are that language deficits can be remarkably isolated early in the course of disease, that damage tends to follow functionally meaningful networks, and that a wide range of regions can be damaged that are not constrained by vascular anatomy. Some of the major challenges include determining the functional status of atrophic tissue, and accounting for functional reorganization that takes place as core language regions degenerate (Wilson, Brambati, et al., 2009).

There are many other etiologies that can result in acquired aphasia, which we will not discuss in detail here. Neurosurgical resection of tumors or epileptogenic foci results in small discrete lesions and focal language deficits that quickly resolve (Penfield & Roberts, 1959; Wilson et al., 2015). However, neurosurgery is, of course, only performed in patients with intractable neurological problems, which may result in reorganization of language prior to surgery (Haglund, Berger, Shamseldin, Lettich, & Ojemann, 1994). This complicates the interpretation of conclusions drawn from these patients. Gunshot wounds can be focal, and obviously the regions damaged are not constrained by vascular anatomy. Pioneers of aphasiology, including Goldstein, Kleist, and Luria, based their work substantially on war-related injuries. However, the changing nature of modern warfare has made gunshot wounds relatively rare.

There are also many clinical syndromes in which language deficits co-occur along with significant other symptoms in other cognitive or behavioral domains. Examples include Alzheimer's disease, Parkinson's disease, traumatic brain injury, and autism spectrum disorder. While studies of each of these syndromes have yielded insights into the neural basis of language, the concomitant occurrence of other deficits makes it challenging to infer brain-language relationships.

THE COGNITIVE NEUROPSYCHOLOGICAL APPROACH

One of the most fruitful approaches to the study of language in patients with acquired aphasia is to investigate language function in individual patients in great detail, determining which functions are impaired and which are spared. We can then make inferences from the pattern of impaired and spared functions to the normal functional architecture of the language system. We refer to this as the *cognitive neuropsychological approach*.

The brain itself need not be a central focus in these kinds of studies. Descriptions of the nature and location of damage are typically included, and possibly computerized tomography (CT) or magnetic resonance imaging (MRI) findings, but these are not usually of central importance. Rather, the critical idea of this approach is that certain patterns of deficits have implications for the functional architecture of the normal language system. The logic is that if the language system can possibly break down in a certain manner (as evidenced by the patient under investigation), then it must be structured in such and such a way. We will illustrate this approach with two examples.

Shapiro, Shelton, and Caramazza (2000) reported a patient named JR who had a selective difficulty in inflecting nouns, but was relatively spared in inflecting verbs. JR had other related deficits, too, but we focus here on the morphological deficit. To document the nature of JR's deficit, the authors designed a set of experiments specifically for this patient. The tasks involved adding and removing inflectional suffixes from nouns and verbs; we focus here only on the tasks that involved adding suffixes.

In order to carefully contrast nominal (noun-related) and verbal (verb-related) morphology, the authors took advantage of two facts about English. First, English has large numbers of words that can function either as nouns or verbs (e.g., *guide* and *sail*). Second, the plural suffix, which applies to nouns, and the third person singular present tense agreement suffix, which applies to verbs, have identical phonological forms, identical allomorphs ([-s], [-z], [-əz]), and identical morphophonemic rules governing allomorph selection. Therefore, any differences observed between performance on noun and verbs could not be attributed to phonological factors or morphology in general.

JR was presented with frames such as the following:

> "This is a guide; these are ___" (guides)
> "These people sail; this person ___" (sails). (Shapiro, Shelton, & Caramazza, 2000, p. 674)

Similar frames were also presented using made-up pseudowords instead of real nouns and verbs, in order to avoid any semantic differences between nouns and verbs.

There were striking differences in JR's ability to inflect nouns and verbs. With real words, he inflected 94% of verbs correctly, but only 73% of nouns. With pseudowords, he inflected 87% of verbs correctly, but only 38% of nouns. By carefully constructing an experiment to probe a specific aspect of JR's language function, the authors were able to demonstrate a *single dissociation*: inflection of nouns can be impaired while inflection of verbs is spared, suggesting that these processes are independent of one another in some respect.

In a follow-up study, the authors built upon this finding, reporting on another patient named RC (Shapiro & Caramazza, 2003). RC was tested with a very similar set of materials to JR, yet he showed a different pattern. With real words, he inflected 76% of nouns correctly, but only 22% of verbs. With pseudowords, he inflected 50% of nouns correctly, but only 21% of verbs. In other words, RC showed the opposite pattern to JR: he showed a selective deficit in inflecting verbs, but was relatively spared in his ability to inflect nouns.

Taken together, these two patients form a *double dissociation*: JR could inflect verbs but not nouns, whereas RC could inflect nouns but not verbs. This is often considered to be more informative than a single dissociation, since it shows that neither process is contained within the other. The authors identify two possible explanations for their results. First, there could be separate morphological processing components for nouns and verbs. Second, there could be separate mechanisms for retrieving syntactic information related to nouns and verbs, which feed into a unitary morphological processing component. In either case, the detailed case studies of the two patients reveal something about the cognitive architecture of the language system. The fact that inflectional morphology can break down for nouns but not verbs, or vice versa, shows that morphological processing related to these major word classes is at least partially segregated (for further discussion of grammatical categories and agrammatism, see Kemmerer, Chapter 30, and Thompson & Mack, Chapter 31, in this volume).

Our second example of the cognitive neuropsychological approach comes from the domain of single word reading. It is well established that reading involves at least two mechanisms: a sublexical mechanism based on regular orthographic-to-phonological mappings, and a whole-word mechanism based on retrieval of (potentially idiosyncratic) item-specific information about the pronunciation of particular words (Marshall & Newcombe, 1973). The former mechanism is required for reading pseudowords (e.g., *hance*), the latter is required for reading exception words (e.g., *choir*), and double dissociations have been robustly documented, showing that the two processes are separable. A question that continues to be debated is the extent to which the whole-word mechanism is tied to semantics. On one view, the whole-word mechanism is always semantically mediated: a word like *choir* is read by mapping the orthographic form *C-H-O-I-R* onto the semantic representation of "a group of singers," and then mapping that semantic representation onto its phonological form [kwaɪɚ] (Plaut, McClelland, Seidenberg, & Patterson, 1996). This view predicts that semantic deficits and deficits in exception word reading should be highly correlated, and indeed this is the case. In particular, patients with semantic dementia, characterized by semantic impairment, almost always present with surface dyslexia, a disorder in which exception words are sounded out (Patterson & Hodges, 1992), and the degree of semantic impairment is correlated with the severity of surface dyslexia (Graham, Hodges, & Patterson, 1994; Woollams, Ralph, Plaut, & Patterson, 2007). An alternative view is that while semantic mediation is always possible, there are also direct links between orthographic representations (i.e., *C-H-O-I-R*) and phonological representations (i.e., [kwaɪɚ]) that do not require semantic mediation (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). We will discuss a paper that provides evidence for this second view.

Blazely, Coltheart, and Casey (2005) investigated two patients with semantic dementia, PC and EM, on a battery of semantic and orthographic tasks. Both patients showed similar deficits in semantic processing: they were similarly impaired in picture naming, and spoken and written word-to-picture matching tasks, with disproportionate deficits on lower frequency items, as is typical in semantic dementia.

However, the two patients differed strikingly in their performance on the orthographic tasks. PC showed a pattern of performance typical of semantic dementia: he made numerous errors when reading exception words, especially lower frequency items, yet he read regular words well, regardless of frequency. On a visual lexical decision task, he also performed poorly, disproportionately so for low-frequency items. In contrast, EM performed nearly flawlessly on reading aloud both regular and exception words, and nearly flawlessly on visual lexical decision. Her pattern of performance is difficult to reconcile with the view that exception word reading is necessarily mediated by semantics, since she showed a similar if not greater semantic impairment than PC, yet her exception word reading was spared. Blazely and colleagues argue that EM demonstrates that there must be a lexical non-semantic route for reading aloud that can be spared even when semantics is impaired. In other words, a single case is sufficient to demonstrate something important about the functional architecture of the reading system (though actually, several other similar patients have been reported; see Blazely et al.. 2005, for references; see also Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24 in this volume).

How then is the typical association of semantic deficits with surface dyslexia to be explained? Blazely et al. (2005) argue that the association is not due to the functional dependence of the two systems, but rather is due to "brain geography": inferior temporal brain regions are thought to be important for semantic processing, and left posterior middle temporal and/or occipito-temporal regions are thought to be important for the orthographic lexicon (Noble, Glosser, & Grossman, 2000). These brain regions are in close proximity and therefore are typically impacted in parallel by the neurodegeneration that underlies semantic dementia.

The two examples we have discussed show how dissociations of language skills in individual patients can provide compelling evidence regarding the functional architecture of the language system. While the studies we discussed do describe the brain regions damaged in the patients investigated, the primary concern is the functional architecture of the language system itself, rather than its neuroanatomy. This is the primary limitation of the cognitive neuropsychological approach. While a carefully documented pattern of performance in a single patient can be sufficient to draw inferences about the necessary architecture of the normal system, the same logic cannot be used to interpret the effect of a lesion in any single patient, due to an unknown degree of individual variability in localization of language function in the brain.

The Syndromic Approach

A second major approach to patient-based studies of the neural basis of language is to define one or more groups of patients, and then to investigate some aspect of language, co-occurrence of symptoms, patterns of recovery, or such, across that group. We refer to this as the *syndromic approach*. There are many different ways that patient groups can be defined, with some of the most common being clinical syndromes (e.g., Broca's aphasia, semantic dementia), clinical features (e.g., agrammatism, apraxia of speech), or underlying pathological causes in PPA patients (e.g., patients who show a specific type of cellular pathology at autopsy). Like the approach discussed in the previous section, the syndromic approach does not necessarily address neural correlates of language deficits directly. To the extent that a clinical syndrome reflects damage to a particular brain region or network (e.g., Broca's area for Broca's aphasia, the anterior temporal lobes for semantic dementia), investigating patterns of performance in patients with that clinical syndrome may shed light on the function of the brain region(s) in question. But as we will discuss in the next section, the relationship between clinical syndromes and damaged brain regions is often complicated. The most important contribution of the syndromic approach is to gain a better understanding of the nature of deficits in clinical populations, which ultimately informs studies that explicitly explore brain-language relationships. We will discuss two studies that exemplify the syndromic approach.

Grodzinsky (1984) investigated the manifestation of agrammatism in languages with different relationships between bound inflectional morphology and lexical categories (noun, verb, adjective). This is an example of a study that shed light on the nature of the clinical syndrome of agrammatism, without explicit consideration of its neural correlates.

Grodzinsky noted that the then-current predominant understanding of agrammatism was centered on the omission of closed-class function words and inflectional morphology (e.g., Goodglass & Berko, 1960). This is a satisfactory basic description of agrammatism in English. However, in English, lexical items have uninflected forms that are well formed both morphologically and phonologically (e.g., *boy, walk*). This is not the case in all languages. In languages like Italian and Russian, uninflected forms are typically well formed phonologically, but not morphologically. For instance, the Italian word for "red" is *rosso* (masculine singular), *rossa* (feminine singular), *rossi* (masculine plural), or *rosse* (feminine plural). The uninflected form appears to be *ross*, and although this would be a phonotactically legal word in Italian, it is not a morphologically well-formed word, and it would never be produced. In Hebrew and other Semitic languages, uninflected forms are neither phonotactically nor morphologically well formed. For instance, the word for "dress" is *simla* (singular) or *smalot* (plural); the root consists of only the three consonants *s-m-l*, and so the root needs to be inflected and cannot be produced alone without violating phonotactic constraints. These observations lead to the following question: What would agrammatism look like in these languages, where omission of bound inflectional morphemes would result in morphologically impossible (Italian, Russian), or phonotactically and morphologically impossible (Hebrew) forms?

Drawing on his own observations of agrammatic aphasia in Hebrew, and data from Miceli, Mazzucchi, Menn, and Goodglass (1983) on Italian and Tsvjetkova and Glozman (1978) on Russian, Grodzinsky found that agrammatic speakers of these languages do not, in fact, produce phonologically or even morphologically impossible forms, as one might expect if agrammatism simply involved the omission of inflectional morphology. Rather, in languages where uninflected forms are not well formed, agrammatic speakers substitute incorrect bound morphemes, rather than omitting them. For instance, a Hebrew-speaking patient produced *nasʔu baʔali* ("drove-3PL my husband"), in which the verb root *n-s-ʔ* ("to drive") is incorrectly inflected for agreement, rather than being produced in its phonotactically impossible root form.

While Grodzinsky's study was based on an extremely limited data set, subsequent systematic studies confirmed that bound inflectional morphemes are substituted, rather than omitted, in richly inflected languages (Bates, Friederici, & Wulfeck, 1987). This line of research is an excellent example of how careful, linguistically informed investigation of language processing in a clinically defined group of patients can shed light on the nature of the clinical syndrome shared by the patients. While these studies do not directly address the neural correlates of agrammatism, they provide crucial information that bears on the interpretation of other studies that do investigate the neural correlates of agrammatism (e.g., Mohr, 1976, discussed in the next section; see also Thompson & Mack, Chapter 31 in this volume).

A second example of the syndromic approach is a study by Bozeat et al. (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000) on nonverbal semantic impairments in semantic dementia. At the time this study was published, the most salient features of semantic dementia were understood to be anomia and verbal comprehension deficits at the single-word level. The researchers suspected that individuals with semantic dementia have conceptual semantic impairments that go beyond language, but the only clear evidence to that effect came from case studies of single patients.

Bozeat and colleagues tested 10 patients with semantic dementia on several semantic tasks that did not involve language in any way. The first was the pictures subtest of the Pyramids and Palm Trees test, in which patients are required to decide which of two pictures (e.g., a palm tree and a pine tree) goes with a target picture (e.g., a pyramid) (Howard & Patterson, 1992). Successful performance requires access to conceptual semantic knowledge (i.e., palm trees and pyramids are both associated with deserts). Two new semantic assessments were also designed for the study: a four-alternative forced-choice semantic association task similar to the Pyramids and Palm Trees test, and a test in which patients were asked to match environmental sounds to their corresponding pictures. Finally, patients' language was assessed with a battery of language tasks.

The authors found that most patients were impaired on all three of the nonverbal semantic tasks, and that the degree of semantic impairment on verbal and nonverbal material was correlated. They concluded that the anomia and word comprehension deficits that are so salient in semantic dementia are in fact just one manifestation of a generalized impairment of conceptual semantic knowledge. The study includes no neuroimaging or discussion of the brain regions that were damaged in the 10 patients studied, but given the well-established finding that semantic dementia follows from atrophy of anterior temporal and ventral temporal regions (e.g., Hodges et al., 1992), it is reasonable to infer that these regions (or some subset of these regions) are critical for conceptual semantic memory independent of any role in language per se.

The studies we have discussed by Grodzinsky (1984) and Bozeat et al. (2000) are excellent examples of the syndromic approach to studies of patients with acquired aphasia. They each reveal new information about the nature of a clinical syndrome. Studies like these are most effective when the patient group under investigation is a "natural kind" (i.e., a grouping reflecting the structure of the world and the phenomena in question), rather than an artificial grouping. Semantic dementia, the defining clinical syndrome in the study by Bozeat et al. (2000), is clearly a "natural kind," with characteristic clinical features, neuropsychological findings, specific patterns of brain atrophy, and, in most cases, a common pathological substrate (Hodges & Patterson, 2007). In contrast, it is less clear that agrammatism is a "natural kind"; indeed, Badecker and Caramazza (1985) argued forcefully that it is not, because few if any patients produce "canonical" agrammatic utterances, there is considerably individual variability, and there is no way to define agrammatism in any way that it is not arbitrary. These issues have been debated vigorously (see Caramazza & Badecker, 1991), but the limitations emphasized by Caramazza, Badecker, and others have not put a stop to syndromic studies, which continue to be a productive line of neurolinguistic research.

THE LESION-DEFICIT APPROACH

The two approaches we have discussed so far are focused more on the characterization of language behavior than directly on brain-language relationships. We turn now to studies in which the neural correlates of language deficits are investigated explicitly. In the lesion-deficit approach, brain damage is characterized through neuroimaging, autopsy, or other methods, and language deficits are characterized through the kinds of tasks and analyses we have discussed already. In this approach, researchers attempt to infer the normal functions of particular brain regions from the patterns of deficits that result when they are damaged.

Single cases can be informative with respect to brain-language relationships, but this is the exception rather than the rule. Broca's first and most famous case, "Tan," may have had a relatively small lesion and an isolated speech production deficit at some point in the course of his neurological history, but by the time Broca examined him, he had been mute for over 20 years, and there had been very substantial progression of not only his brain damage, but also his symptoms (Broca, 1861). When Broca examined the brain at autopsy, he found that besides the damage to the inferior frontal gyrus, there was also significant damage to the middle frontal gyrus, precentral gyrus, anterior parietal regions, superior temporal gyrus, insula, and underlying white matter. “Tan” was not just unable to speak; he also had motor symptoms, including paralysis of the right hand and right leg. Moreover, substantial comprehension and cognitive deficits were evident, even based on Broca’s rather cursory examination. Broca’s inference that the inferior frontal gyrus specifically was responsible for an isolated speech production deficit was largely speculative and was not supported by any such specific relationship in the patient as Broca observed him. And indeed, this finding has not stood the test of time, as we will discuss shortly.

In contrast, some single cases have yielded novel and enduring findings. A good example is Liepmann’s (1898) description of a patient with pure word deafness (i.e., auditory agnosia for words) due to a unilateral lesion (see also Geschwind, 1965). Pure word deafness is a clinical syndrome in which words cannot be understood, despite hearing being otherwise intact. Liepmann showed that the patient’s lesion, which was located subcortically in the left temporal lobe, had destroyed fibers from both left and right auditory cortices, preventing auditory input from reaching the posterior temporal language region (i.e., Wernicke’s area). Patients with pure word deafness have relatively normal speech, in contrast to the jargon aphasia that results when Wernicke’s area itself is damaged. Liepmann’s single case study suggests then that (1) associations between auditory word forms and meanings are carried out only in the left hemisphere; and (2) auditory input from primary auditory cortex in either hemisphere is sufficient to associate word forms with their meanings (because pure word deafness arises only when auditory input from not only the left but also the right hemisphere is unavailable, due either to a subcortical lesion or to bilateral lesions). Liepmann’s case provides an example of how informative a single patient can be with respect to brain-behavior relationships. What makes this possible is that the language deficit is circumscribed and well characterized, the lesion is small, and the effects of the lesion are understood in terms of the anatomical regions and functional pathways involved. It is rare for all of these criteria to be met in a study of a single case (see also Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume).

More often, patients with acquired aphasia have larger lesions or degenerative processes that affect multiple brain regions and pathways. Therefore, the majority of studies of brain-language relationships have investigated lesion locations in groups of patients sharing common clinical or linguistic features. The most straightforward approach to a lesion-deficit study is to create an overlay of the lesions of patients with a common clinical syndrome or a common pattern of performance on some task, in order to determine which brain region(s) are damaged in all (or at least most) of the patients. The commonly destroyed region can then be associated with the syndrome or linguistic behavior in question, and it can potentially be inferred that the region in question is critical for the language process(es) that is (are) impaired in the syndrome under investigation.

These studies began to appear with the advent of CT imaging in the 1970s and then structural MRI in the 1980s. Some of the early studies looked at lesion overlays of classical aphasic syndromes. For example, Naeser and Hayward (1978) created lesion overlays of patients diagnosed with Broca's aphasia, Wernicke's aphasia, conduction aphasia, transcortical motor aphasia, and global aphasia. There were three to four cases of each type. The lesion patterns were broadly in accordance with expectations based on the classical model (Wernicke, 1874; Lichtheim, 1885), but the lesions were typically large in extent. Basso, Lecours, Moraschini, and Vanier (1985) looked at CT scans of 267 patients with left hemisphere lesions, of whom 207 had cortical lesions. Of these 207 patients, they found that 171 had aphasia syndromes that were in accord with expectations based on classical theory, whereas 36 patients did not: they had aphasia despite damage that spared language regions, or no aphasia despite damage to language regions, or a different type of aphasia than would be expected from the location of the damage. It is encouraging how many patients had language disorders that were consistent with the classical model, yet the 36 patients with unexpected findings raise challenging questions about individual variability in language localization, cortical plasticity, possible functional deficits in addition to structural deficits, and so on, that remain the subject of active research.

Probably the most important study from this period is Mohr's (1976) seminal paper entitled "Broca's Area and Broca's Aphasia," which comprises two complementary lesion overlay studies. Mohr's clinical experience as a stroke neurologist had led him to question the widely accepted relationship between damage to Broca's area (which he defined quite narrowly as the pars opercularis of the left inferior frontal gyrus), and the clinical syndrome of Broca's aphasia, defined in the way the term is generally used in the literature: by halting, effortful speech characterized by agrammatism, short words and phrases, disordered motor planning and/or execution of speech sounds, stereotypies, impaired written language, and relatively spared comprehension except for more syntactically complex constructions. Mohr took a simple and elegant approach to showing that the assumed relationship between damage to Broca's area and Broca's aphasia, does not hold. First, he documented the clinical syndromes resulting from lesions restricted to Broca's area. Then, he overlaid the lesions of patients diagnosed with the clinical syndrome of Broca's aphasia. If the traditional view were correct, these two approaches should have involved the same patients and the same lesion locations, but this did not turn out to be the case.

Mohr examined 12 patients who had lesions that were relatively restricted to Broca's area (i.e., the posterior part of the left inferior frontal gyrus), as shown by neuroimaging or autopsy. The patients varied considerably in their clinical deficits immediately after stroke, ranging from barely detectable disturbances of speech to complete mutism. But all recovered quickly, with most passing for normal within a month or two, and agrammatism was rarely seen even acutely. Not one of these patients experienced a persisting Broca's aphasia.

Then, Mohr identified 10 patients who satisfied the criteria for the clinical syndrome of Broca's aphasia some months after their stroke. Using neuroimaging or autopsy, he showed that in each patient, there was always infarction not just of Broca's area, but of nearly all of the territory of the upper division of the middle cerebral artery, that is, posterior inferior frontal regions, the insula, the precentral and postcentral gyri, anterior parietal regions, and underlying white matter. In other words, damage needed to extend well beyond Broca's area to cause the clinical syndrome of Broca's aphasia.

This study is an excellent example of the power of the lesion overlay approach to document the language deficits that result from lesions to a given brain area, and the brain regions that must be damaged for a given pattern of deficits to result. It is worth noting that this study was made possible by two things: the availability of CT scans, and Mohr's role on the stroke service of a large hospital. The two dozen patients discussed in the paper were selected from hundreds, if not thousands, of stroke patients (see also Mohr et al., 1978).

Another important lesion overlay study employed two groups of patients in a different way. Dronkers (1996) sought to identify the brain region(s) where damage was associated with the clinical syndrome of apraxia of speech, an impairment in planning and coordinating speech movements (see, in this volume, Tremblay, Deschamps, & Dick, Chapter 15; Ziegler, Schölderle, Aichert, & Staiger, Chapter 18). She identified one group of 25 chronic stroke patients diagnosed with apraxia of speech, and a second group of 19 patients who were similar in some respects, but did not present with apraxia of speech. She overlaid the lesions of the 25 patients with apraxia of speech, and found that all 25 lesions included a region in the left anterior insula (specifically, the superior part of the precentral gyrus of the insula). She then overlaid the lesions of the 19 patients without apraxia of speech, and found that none of their lesions involved that region of the insula. Because none of the lesions in the control group without apraxia of speech overlapped with the area of damage common to the 25 individuals with apraxia of speech, she concluded that damage to the left anterior insula is necessary and sufficient to cause apraxia of speech, and that this region is therefore essential for coordinating speech articulation.

The inclusion of the control group without apraxia of speech is critical in this study, especially since the anterior insula is adjacent to the middle cerebral artery, and is commonly damaged in stroke. However, Dronkers's findings have been questioned by other researchers, most notably Hillis et al. (2004), who studied 80 acute stroke patients and found that apraxia of speech was more robustly associated with infarction or hypoperfusion of Broca's area than of the anterior insula. Hillis and colleagues argued that it is important to study patients in the acute phase, because deficits due to small lesions may resolve quickly. Bonilha and Fridriksson (2009) questioned Dronkers's findings from another point of view: they argued that the association reported by Dronkers is not due to damage to the anterior insula, but rather is due to damage to the immediately medially adjacent white matter fiber pathway connecting frontal and temporal language areas. The role of the insula in speech production, and in the clinical syndrome of apraxia of speech, continues to be debated. Our purpose here is simply to examine and explain the logic of Dronkers's study (in particular, the control group without apraxia of speech) and the kinds of objections that may still arise.

Many language deficits are graded, not discrete. So while apraxia of speech is typically conceived as a clinical feature that is either present or absent, other deficits such as impaired lexical access occur in essentially all patients with aphasia, but to different degrees. In these cases, it is not possible to visually compare two groups of overlaid lesions, such as in the Dronkers study, where one group presented with the symptom and the other group did not present with the symptom. When the behavioral deficit is present over a range of severity, a study can still utilize the lesion-deficit approach, but it requires modern computerized procedures. Specifically, the related techniques of voxel-based morphometry (VBM) (Ashburner & Friston, 2000), and voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003) are used to investigate brain-language relationships with continuous behavioral variables. Both approaches involve computing relationships between damage and continuous behavioral variables at each voxel (three-dimensional pixel) in a brain image. VBM is used for degenerative cohorts in which atrophy is graded, so at each voxel a correlation coefficient is calculated between degree of atrophy and degree of behavioral impairment. VLSM applies to cohorts in which lesions are modeled as discrete, such as stroke, so at each voxel a statistical comparison is made between patients whose lesions do and do not include that voxel. The development of VLSM and VBM has advanced the lesion-deficit approach in other ways, too, such as enabling confounding variables (e.g., age, gender, time post-onset) to be factored out as covariates when examining language-brain relationships. Bates et al. (2003) provided a basic proof of principle, showing that reduced fluency and comprehension deficits were associated with damage to distinct regions, specifically the anterior insula or the dorsal white matter tract connecting anterior and posterior language areas for fluency, and the posterior middle temporal gyrus for comprehension (Figure 2.1).

VBM and VLSM are capable of revealing distinct neural correlates, not only of distinct language processes such as fluency and comprehension, but also of closely related parts of the same language process. For instance, Wilson, Henry, et al. (2010) showed in a neurodegenerative cohort distinct brain regions where atrophy was correlated with prevalence of phonemic paraphasias and with prevalence of distortions, which reflect two different stages of speech production. In another study using VLSM, Schwartz et al. (2009) showed that semantic errors in picture naming (e.g., *horse* for *goat*) are associated with damage to the anterior and middle portions of the middle temporal gyrus. A particularly interesting feature of this study was that the authors included a covariate of performance on nonverbal semantic tasks (the same two picture-association tasks that were employed in the study by Bozeat and colleagues [2000] described earlier). By showing that damage to the anterior to mid-middle temporal gyrus predicts semantic errors above and beyond any effect it may have on conceptual semantic processing, Schwartz and colleagues were able to argue that this brain region has a role in a specific stage of lexical access, namely lemma retrieval, where an abstract pre-phonological word form is retrieved. Several recent studies have shown that VLSM can also provide informative analysis of measures of underlying language-processing constructs derived from factor

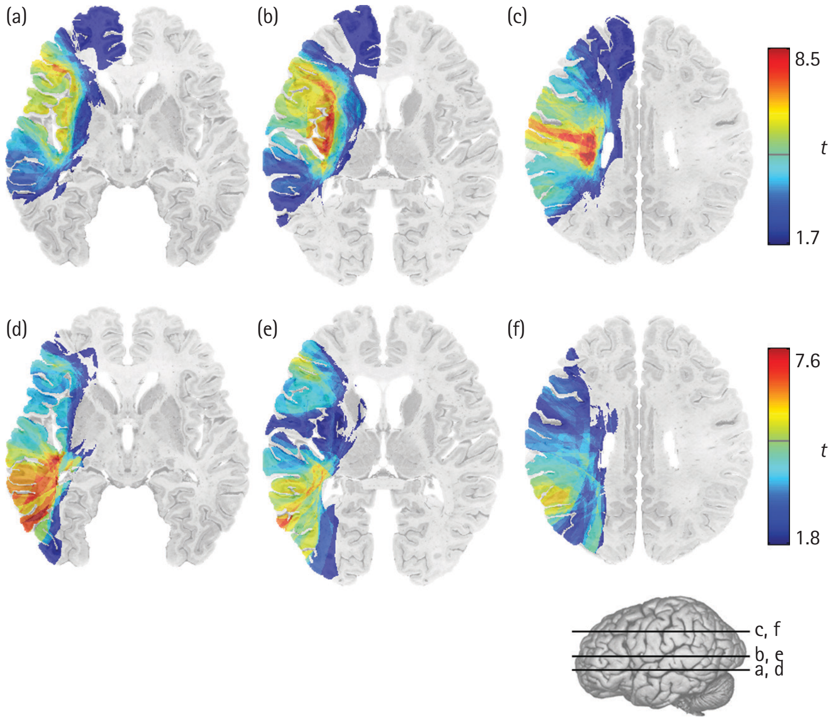

FIGURE 2.1. VLSM maps computed for fluency and auditory comprehension performance of 101 individuals with post-stroke aphasia. These maps are colorized depictions of *t*-test results evaluating patient performance on a voxel-by-voxel basis. Patients with lesions in a given voxel were compared to those without lesions to that voxel on measures of fluency (a, b, c) or auditory comprehension (d, e, f). Lesions to voxels shown in hot colors (red, orange) had a highly significant impact on fluency (top panels) or auditory comprehension (bottom panels).

Source: Reproduced from Bates et al. (2003).

analysis (Mirman et al., 2015), principal components analysis (Butler, Lambon Ralph, & Woollams, 2014), or parameterization of computational models (Dell, Schwartz, Nozari, Faseyitan, & Coslett, 2013).

In their basic form, VBM and VLSM are mass univariate approaches, meaning that the statistical computation at each voxel does not take into account damage to the rest of the brain. This is a significant limitation, since in reality there is always damage extending beyond any single voxel under consideration, and the damage beyond any given single voxel presumably also contributes to any behavioral deficits. Moreover, the patterns of involvement of other voxels are nonrandom, since they reflect underlying factors related to the etiology, such as vascular anatomy in the case of stroke (Inoue, Madhyastha, Rudrauf, Mehta, & Grabowski, 2014; Mah, Husain, Rees, & Nachev, 2014). Therefore, regardless of how strongly damage to any voxel is associated with the behavioral deficit in question, it cannot be concluded that the voxel is really critical for the behavior. To account for the contribution of voxels other than the one under consideration, it is necessary to carry out multiple regression, in which damage to multiple brain regions is entered into a predictive model. However, the number of voxels will always be much larger than the number of patients, so only a subset of regions can be considered, typically motivated by a priori expectations. For instance, Wilson et al. (2015) showed in a neurosurgical cohort that damage to the temporal pole does *not* contribute to naming deficits once damage to the basal temporal language area is taken into account. Studies in which larger numbers of regions have been entered into statistical models have generally not yielded clear results (e.g., Caplan et al., 2007), because the more regions that are entered, the more patients are required to distinguish between the contributions of the different regions.

Another approach to the mass univariate limitation is to think differently about how to interpret the meaning of significant findings in VBM and VLSM analyses. Rather than interpreting them as showing that any given voxel is involved or not involved in a language process, we can instead think of these as methods for determining whether there is a nonrandom relationship between the location of brain damage and a particular type of language deficit. Permutation testing, in which the available behavioral data are scrambled among the patients under investigation and so randomly associated with lesions, can be used to empirically generate the distribution of voxelwise lesion-symptom associations under the null hypothesis that there is no relation between location of damage and the language variable of interest (Kimberg, Coslett, & Schwartz, 2007; Wilson, Henry, et al., 2010). Then, the real data can be compared to this null distribution to determine whether there are particular regions in which association is stronger than would be expected based on chance. VBM or VLSM statistical maps should therefore properly be interpreted not as showing whether any given voxel is critical for a language function, but as showing that lesion location is predictive of deficits.

Recently, several studies have moved beyond the mass univariate approach by using machine-learning methods to investigate relationships between distributed patterns of damage and aphasic syndromes or symptoms (Wilson, Ogar, et al., 2009; Xing et al., 2016; Yourganov, Smith, Fridriksson, & Rorden, 2015; Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). Another major focus of current research is on better characterizing the nature of brain damage, as well as potential reorganization, in patients with acquired aphasias. CT and structural MRI provide relatively clear delineation of core lesions; however, it is becoming increasingly apparent that damage to any one region often has implications for brain regions that appear to be structurally intact. These changes may include hypoperfusion (reduced blood flow and/or metabolic function) (Hillis et al., 2002; Metter et al., 1989), degeneration of white matter tracts (Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Wilson, Galantucci, et al., 2011), diaschisis (dysfunction of adjacent or functionally connected regions due to lack of normal inputs from the damaged region) (Mummery et al., 1999), and other functional abnormalities (Warren, Crinion, Lambon Ralph, & Wise, 2009). Better understanding the complex set of changes that take place in the brains of individuals with acquired aphasia requires a multimodal neuroimaging approach, using techniques such as structural and functional MRI, perfusion MRI, diffusion tensor imaging, and positron emission tomography.

CONCLUSION

Patients with acquired aphasias due to stroke, neurodegenerative disease, neurosurgery, and other etiologies have yielded a great deal of information about the cognitive and neural architecture of the language system. Cognitive neuropsychological investigations of individual patients can lead to strong inferences about the functional architecture of the language system. Studies of patients defined by a clinical syndrome can also be informative in understanding the nature of the syndrome, to the extent that the syndrome is a "natural kind." Lesion-deficit studies examine the relationships between damage to different brain regions and resulting language deficits.

It is always challenging to make inferences about the functional roles of specific brain regions. Only rarely is brain damage confined to a single brain region. Similarly, only rarely do patients present with a deficit in a single aspect of language processing. More often, multiple regions are damaged, and there are consequences for multiple aspects of language processing, making it challenging to relate regions and functions on a one-to-one basis. Patients recover to varying extents from strokes and from neurosurgical lesions, implying that there is considerable cortical plasticity, so when we examine a patient with a lesion we are generally dealing with a language system that has been reorganized to some extent. Finally, while it is clear that brain regions are not equipotent when it comes to language, it is also surely not the case that each region simply performs a single function. While all researchers intuitively understand the limits of modularity, all three of the approaches that we have discussed are predicated on functional and/or neural modularity. A major challenge in the coming decades will be to develop methods and approaches that are better able to reveal the more complex reality of brain-language relationships. Despite these and the other challenges discussed in this chapter, patient studies continue to offer some of the clearest and most persuasive data on the cognitive architecture and neural basis of language.

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CHAPTER 3

ELECTROPHYSIOLOGICAL METHODS IN THE STUDY OF LANGUAGE PROCESSING

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Introduction and History

An interest in how language processing unfolds and how it is implemented in the brain is long-standing, yet the complexity of language and its absence (at least in complete form) in nonhuman animals has rendered the study of language especially difficult. Language comprehension, in particular, has no necessary behavioral consequence, so cognitive studies of language have resorted to developing language-related tasks (e.g., naming, lexical decision) in order to obtain behavioral measures. This approach has yielded valuable results, giving insights into the nature of underlying cognitive mechanisms, but comes with unavoidable limitations, as it reduces ecological validity and ultimately provides no direct information about the processes occurring in the period between stimulus presentation and the behavioral response. Measurements of electrical brain activity (as well as other types of neural measures) have played a critical role in bridging this gap, as they can trace processing over time with a high degree of accuracy without requiring an overt response (e.g., Kutas & Van Petten, 1994). Accordingly, they have been used to add weight to or to falsify behaviorally posited arguments and also to provide completely novel insights into the cognitive and neural bases of language.

The origins of human electrophysiology can be traced back to the 1920s, when the first electroencephalogram (EEG) was recorded from a human participant. Prior to this, recordings of electrical activity had been taken from the brains of nonhuman mammals, but it wasn't until German neurologist Hans Berger (1873–1941) took an interest in connecting higher mental processes to their underlying physiological mechanisms that these methods were extended to human testing (Millett, 2001). The first successful human recording came in 1924, when electrodes were placed under the scalp of a patient who had had part of his skull removed as part of a medical procedure, but the findings of this and other early studies (including those from participants with intact skulls) were not published until 1929 (Berger, 1929), and it was not until the mid-1930s that the EEG was recognized as a valuable diagnostic tool in clinical neurology. In more recent years, this method, along with the derivation of event-related potentials (ERPs), has been used to great effect in cognitive neuroscience research.

Human electrophysiological measures are noninvasive, recording brain signals through the use of electrodes placed over the head and on the face and extremities. These electrodes pick up the electrical potentials that are an inherent part of neural communication. Neural transmission involves the flow of ions, which carry a charge, across the cell membrane, resulting in changes in the electrical potential, the attractive force that dictates the extent to which charged particles feel the urge to move. In a canonical neural transmission event, an electrical signal, originating in the cell body of a transmitting neuron, travels rapidly down the axon via saltatory conduction. This action potential causes the release of neurotransmitters, which bind to the dendrites of a receiving neuron, causing a change in its electrical potential. Depending on the neurotransmitter that is released, this change in potential can make the receiving cell more likely to fire (an excitatory postsynaptic potential, or EPSP) or less likely to fire (an inhibitory postsynaptic potential, or IPSP). These potential changes can be detected at a distance, forming the signal captured by the EEG recording (for a detailed discussion, see Nunez & Srinivasan, 2006).

Because the strength of the electrical potential falls off with distance, the ability to pick up potential changes depends on the sensitivity of the recording equipment and the size of the potential change. The generation of signals of sufficient strength to be detectable at the scalp using modern recording equipment requires that large numbers of neurons be subject to EPSPs or IPSPs in relative synchrony, so that their potentials can add. Moreover, in order for the potentials to sum to create a large "equivalent dipole" that is measurable at a distance, the neurons must be arranged in what is known as an open field, wherein they are all pointing in a similar direction. If the neurons are instead arranged in a closed field, as is true for a number of subcortical structures, the potentials generated by individual neurons cancel one another so that there is no detectable activity at the scalp (see Allison, Wood, & McCarthy, 1986).

Luckily for the study of human cognition, the cortex provides good conditions for electrophysiological recordings. Cortical pyramidal cells are generally arranged in an open field, tend to become active in relative synchrony, and are close to the scalp, meaning they are more easily picked up by scalp electrodes (see Luck, 2014, Chapter 1, for a more detailed explanation of this). Although in some circumstances, action potentials can be picked up, it is mostly postsynaptic currents that are measured, as they are dipolar, so their electromagnetic field falls off less rapidly than that of action potentials, which are quadrupolar (Ilmoniemi, 1993). Thus, the EEG provides a direct measure of neural activity, much of which originates from postsynaptic changes in cortical pyramidal cells. The signals that are detected from the cortex are very small, and therefore must be amplified. Moreover, along with brain activity, other biological signals are picked up, such as muscle activity, eye movements, and the heartbeat (as, even though these signals are produced farther away from the sensors, they are much larger than brain electrical activity). Thus, as will be discussed in more detail later, these potential artifacts must be avoided or removed in order to allow uncontaminated extraction of the neural signals that are of interest for most experimental designs.

EVENT-RELATED POTENTIALS: RECORDING CONSIDERATIONS

The EEG signal is continuous and is characterized by large, rhythmic fluctuations across different frequency bands. Although these signals have clinical utility and are sometimes measured to address cognitive questions (see, e.g., Bastiaansen, Mazaheri, & Jensen, 2012; Mathewson et al., 2011), most cognitive studies are interested in the neural events that immediately follow a stimulus or that lead up to a behavioral response. These time-locked (and phase-locked) neural responses—or event-related potentials (ERPs)—are therefore extracted from the continuous EEG. Traditionally, these signals are separated from the background "noise" of electrical activity that is not temporally aligned with events of interest via averaging (but see, e.g., Makeig, Debener, Onton, & Delorme, 2004, for alternative approaches). By taking the mean of a number of segments of the EEG aligned in time with the presentation of a stimulus (to create a stimulus-locked ERP) or the execution of a response (a response-locked ERP), it is possible to measure brain activity that is yoked to that event, with an improvement of signal to noise that increases with the square root of the number of trials that are averaged together (assuming consistent signal and random noise).

In designing an ERP study, the primary goal is generally to obtain stable within-subject responses that can be readily interpreted with respect to experimental conditions of interest. In the service of this goal, it is critical to plan ahead to avoid confounds and/or to have strategies for dealing with confounds and issues that cannot be avoided. One of the primary considerations is the number of participants and the number of items per condition, and these factors trade off with one another. In a typical language experiment in which a fairly large effect is expected, trial numbers would typically be around 25–60 items in each critical condition of interest, and approximately 20–30 participants would be run. However, this number of trials may be unrealistic in designs that use long texts (where large numbers of trials may induce participant fatigue) or that target language phenomena with inherently limited numbers of items (where increasing trial numbers would entail repetition, a manipulation that is known to affect processing—and the resultant ERP waveform—in multiple ways). More limited numbers of trials, including even single-item designs, can be used if more participants are run and/or appropriate analytical approaches are used in order to keep power high (e.g., Laszlo & Federmeier, 2011, 2014).

Another critical consideration for designing an ERP experiment is the choice of the reference electrode. The electrical potential is the force that compels a charged particle to move from one place to another; it thus inherently involves a comparison across two locations. In practice, to reduce contributions of external noise sources to recordings, EEG techniques generally make use of a minimum of *three* electrodes and differential amplification, amplifying the difference between an active electrode and an electrical ground and a reference electrode and that ground (see discussion in Luck, 2014). This double subtraction serves to remove noise that is commonly experienced by all electrodes, leaving just the signal of interest, as a difference between each active location and a common reference electrode (or set of electrodes). Obviously, the signal recorded from an active electrode is therefore importantly shaped by the choice of reference. For example, the fact that the recorded signal is a subtraction is part of the reason that the absolute polarity (positive or negative) of the measured voltage does not provide any information about the nature of the underlying cognitive or neural processes involved.

Ideally, the reference would be placed somewhere “neutral” that picked up neither brain signals nor artifactual activity from the body. In practice, no such sites exist. Thus, the choice of reference electrode is dictated by locations that are practical and that are likely to provide the least distortion to signals of most critical interest. Common reference sites include the nose and the mastoid processes (bony sites behind the ear) or earlobes. When mastoid/earlobe references are used, the reference is the average of the activity across the two electrodes, to avoid creating lateralized biases in the recording. Instead of picking a particular reference site, some researchers create what is known as an *average reference*, in which the average of activity across all electrodes is subtracted from each electrode. This approach tends to highlight activity that is localized to only a few electrode sites and to reduce effects with a widespread distribution (including several of the most commonly studied language-related components). This approach is obviously also very sensitive to the overall number and distribution of electrode sites used.

All of these reference types pick up brain activity, and if the neural activity of interest is near the reference electrode, it may be subtracted out. Thus, although the use of the average mastoid/earlobe reference is perhaps most common, especially for studies of language, different subfields have come to use different typical reference sites to allow the best characterization of the responses of most interest in that literature. When designing an ERP experiment, therefore, it is critical to note what reference is used in the literature that forms the background for the work, and generally it is preferable to use that reference. Comparisons of effects are difficult, if not impossible, across different reference configurations (although in some cases, data can be re-referenced).

Other choices that need to be made include the type, number, and distribution of electrode sites. Electrodes have traditionally been passive sensors, made of electrically reactive metals like silver/silver chloride or tin, which carry signals to an amplifier some distance away. However, some modern systems build the amplifier into the electrode (in what has been termed *active electrode systems*), as the shorter distance between the sensor and the amplifier can reduce noise in electrically compromised environments and/or under conditions of high impedance. These two types of electrodes have trade-offs in terms of cost, ease of use, and performance (for a direct comparison of the performance of passive and active electrodes under different recording conditions, see Laszlo, Ruiz-Blondet, Khalifian, Chu, & Jin, 2014).

Up to 256 electrodes can be used (beyond this, there is no further gain in spatial precision), but large arrays come with costs in terms of preparation time, chances of bad data from one or more sensors, bridging between electrodes, and processing complexity. In language studies, arrays of 20–60 electrodes are most common, and even studies that use larger arrays often select or group electrodes to form coarser regions of analysis (raising questions about the utility of having initially obtained high-density recordings). Better than having large numbers of electrodes is yoking the number of electrodes to the design and question of interest. For example, broadly distributed and well-characterized responses can be measured with a small, well-chosen array of electrodes, and the savings in preparation time for each participant can thereby allow for designs with much higher numbers of participants and enhanced ability to look at responses to even individual items (see, e.g., Laszlo & Federmeier, 2011).

Finally, because the brain signals are small and attenuated by passing through the meninges, skull, skin, and so on, EEG data must be amplified. The process of amplifying and then sampling the data changes that data in ways that are critical to understand when carrying out EEG recording. All amplifiers have a dynamic range, and it is important that the amplifier gain be set so that responses are likely to stay within that range, to prevent "blocking" (in which the amplifier becomes insensitive to changes in potentials and registers just a maximum or minimum measurement), and that, if blocking occurs, those trials be removed from the data. As well as amplifying the neural signals, the amplifier also acts as a filter, meaning that it removes signals with certain frequency characteristics (i.e., low-pass filters that attenuate high-frequency signals, and high-pass filters that attenuate low-frequency signals). Filtering is a complex topic, and it is critical for researchers using EEG/ERP methods to familiarize themselves with how filtering works and what types of signal distortions it can create (see, e.g., Chapter 5 in Luck, 2014). As general guidelines, language researchers should be aware that commonly studied language responses contain frequencies between about 0.1 and 20 Hz, so filters that extend into this range run the risk of attenuating or distorting effects of interest (see, e.g., Tanner, Morgan-Short, & Luck, 2015), and that the analog filtering implemented in an amplifier is different from digital filtering of the sampled data. The greater complexity and reduced frequency precision of analog filters generally make it preferable to record the data with limited filtering and to apply digital filters later, as necessary. However, some filtering is necessary at the stage of amplification, in order to avoid the problem of aliasing, as described next.

The amplifier provides a continuous, analog signal. To obtain data from this signal, therefore, it must be sampled—that is, transformed into a digital signal with individual pairings of time points and voltages (at some level of precision). The sampling rate describes how often such samples are taken. The minimum sampling rate that should be used is given by the Nyquist criterion, which states that the sampling rate must be at least twice as fast as the highest expected frequency in the signal to avoid the possibility of artificially creating a low-frequency signal in the data by undersampling a high-frequency one (i.e., aliasing) (Luck, 2014). Filtering is therefore used at the stage of amplification to limit the high-frequency content of the sampled signal (and also to prevent artifacts from low-frequency drift). Because the cutoffs of analog filters are gradual, in practice the sampling rate must be more than twice the low-pass frequency set on the amplifier. Thus, with sampling rates of 250 Hz or more, frequencies up to 100 Hz can be safely sampled.

Event-Related Potentials: Experimental Design and Analyses

To collect interpretable ERPs, several important design considerations should be kept in mind. First, the exquisite temporal sensitivity of ERPs means that timing must be a critical consideration in the experimental design. Sensory ERPs are elicited in response not only to stimulus onsets, but also to offsets and, indeed, any perceptible change in the stimulus; thus, it may be desirable to try to time stimulus presentation so that offset potentials, for example, fall outside the range of other components of interest. Along the same lines, it should be noted that forward and backward masks both elicit their own ERP responses, which are likely to overlap substantially with those of the critical stimulus. Since masking is sometimes used in behavioral paradigms to try to target "early" aspects of processing, which ERPs naturally reveal, it may not be necessary in many ERP adaptations of traditional designs—and, when masking is used, the resulting ERPs must be analyzed and interpreted with care. Responses, including the preparation to make a response, also elicit ERPs. Because ERPs can be used to measure cognition without the need for an overt response, it is often desirable to design ERP experiments so that behavioral responses are not elicited to critical stimuli—or, if needed, are delayed (see Van Vliet et al., 2014, for a discussion of the difficulties created by response-related activity in cognitive ERP experiments). ERP responses are also elicited by anticipation of a stimulus or response. Many ERP designs therefore introduce temporal jitter into parts of the experimental design, such as between a fixation point and the first word of a sentence, to reduce the contribution of activity related to this kind of anticipation to the average ERP.

The temporal sensitivity of ERPs allows for the study of processes unfolding at many different time scales. Often in the study of language comprehension, researchers will time-lock to the onset of a critical word; however, one can also time-lock to the onset of a critical phoneme or morpheme, to a "gap" in a syntactic structure, to a phrase, clause, or sentence boundary, to the presentation of a probe stimulus, or to a response—an option that is often used in production research (Ganushchak, Christoffels, & Schiller, 2011). At the same time, the need for a time-locking point makes it more difficult to study processes whose onset is unknown, variable, or extended in time (e.g., inference-drawing, prediction). Often researchers can only look at downstream consequences of these processes with ERPs (e.g., the apprehension of an unpredictable word). However, the measurement of slow potentials and examination of non-time-locked activity in the time-frequency domain promise to open new avenues of exploration for these types of processes as well (e.g., King & Kutas, 1995; Rommers et al., 2017).

Second, one of the advantages of ERPs is their sensitivity to many, sometimes subtle, variables. However, the fact that ERPs are a sensitive measure and one that picks up activity across the entire time course of processing makes them also good at revealing confounds in experimental designs. Therefore, when designing an ERP experiment, it is critical to control for the full range of perceptual variables that could differ across stimuli, for the probability of stimulus categories, for all aspects of response-related activity (e.g., timing of response preparation, hand used to respond, type and probability of errors, etc.), and for various aspects of what participants anticipate, what they are attending to, and what strategies they are employing. When possible, the use of perceptually identical critical stimuli and/or of identical contexts is ideal. When not possible, extraneous factors should be matched as closely as possible, or the study should be designed so that the effects of potentially confounding variables can be directly examined. For language experiments in particular, it is important to consider not only word length, part of speech, and frequency (as is also common in behavioral designs), but also concreteness and neighborhood density, which often have larger effects on language-related brain responses than do frequency and length (see, e.g., Kounios & Holcomb, 1994; Laszlo & Federmeier, 2009). For sentences, length, structure, and complexity are important, and the position and predictability (e.g., cloze probability; Taylor, 1953) of critical words in the sentence must be controlled. When words are being presented in a series, one must consider the possibility of influences from words that immediately follow critical words, as ERP responses elicited to those subsequent words are likely to overlap in time with the ERPs to the word of interest. Finally, many aspects of the brain response are highly sensitive to repetition, at all levels; thus, when necessary or desirable, repetition must be used with care in experimental designs.

As a general guideline, caution should be used when ERPs are being directly compared across different participant groups (e.g., young adults and older adults), different sentence positions (e.g., sentence-initial, sentence-intermediate, and sentence-final words), or different screen positions (e.g., left and right visual field). Across such comparisons, the basic morphological characteristics of the waveform are likely to differ, meaning it is difficult to align the waveforms appropriately to interpret effects. In these cases, it is better to compare the patterns of effects that are measured within a group or position. Similar problems arise when directly comparing conditions with different configurations of componentry (e.g., a condition that elicits just an N400 versus one that elicits both an N400 and a P600) or that are associated with response differences. Comparisons across average ERPs based on very different numbers of trials can also be problematic, due to differences in noise.

ERP study designs must also keep in mind the need to avoid contamination of the data by various types of artifacts. Perhaps the most common artifacts are those that come from eye movements and blinks. The eye is an electrical dipole, which means that any movement of the eyes creates large electrical signals that can overpower the smaller brain signals, especially at sites over the front of the head, where eye movements have more of an effect. The most common method of minimizing these artifacts is through prevention: by asking participants to limit eye movements and blinks and by designing stimuli and paradigms to make these less likely. ERP experiments using visual words, for example, generally present them one at a time in the center of the screen, to mitigate the need to move the eyes (although some recent work has been successful at recording ERPs during natural reading; see Hutzler et al., 2007). Similarly, ERP experiments using pictures or scenes generally size these to allow them to be apprehended without scanning. However, some participants have difficulty controlling these responses, and some researchers worry that inhibiting blinks and eye movements can be a type of task in and of itself and therefore may affect the resulting data. When blinks and eye movements do not invalidate the experimental manipulation (e.g., a blink during a critical time window that means a participant likely didn't see the stimulus, or a saccade that indicates that a participant likely foveated a lateralized stimulus), corrections can sometimes be applied that aim to selectively remove the artifactual activity, yielding usable trials (see Croft, Chandler, Barry, Cooper, & Clarke, 2005, for a discussion). As these methods vary in any given circumstance as to how well they can remove the artifacts successfully while not affecting the data in any other way, they should be used with care and their success assessed empirically whenever they are applied. Other sources of artifact include muscle activity, which shows up as high-frequency bursts and should be prevented when possible but can often be filtered out during post-processing, and heartbeat (EKG), which can sometimes be prevented by keeping electrodes away from locations with a palpable pulse, but which, when not preventable, will often be reduced by averaging.

ERPs are commonly visualized as waveforms—plots of voltage over time, one for each recording site. Each waveform is made up of a series of positive- and negative-going voltage deflections (when well studied, sometimes called *components*), relative to a baseline. Baselining consists of setting the mean voltage in each condition to zero in some time window, generally 100 milliseconds (ms) or more immediately prior to the time-locking point. It is done to remove artifactual slow activity (e.g., DC offsets from skin potentials) that might differ across conditions; because these can vary by electrode, baselines are generally computed separately for each. ERPs are a highly multidimensional measure, which can yield information about when activity patterns or effects occur, about the size of those responses, and about their scalp topography (which is not the same as the spatial location of their neural sources). Analyzing ERP data thus requires selecting measures to address the question(s) of interest and then making specific choices about how those measures will be obtained.

One of the most basic questions that can be asked with ERPs is whether there is a difference in waveform amplitude across conditions. Such questions are answered by measuring either mean voltage or peak (maximum/minimum) voltage in one or more time windows at one or more active electrode sites. Mean amplitude measures are often preferred to peak amplitudes because peak amplitude measures are more dependent on waveform morphology (e.g., some effects don't have a clearly defined peak) and more susceptible to noise. However, when multiple, differentiable responses occur in rapid succession (as, for example, is often the case for early sensory responses), peak amplitude measures may provide a means of separating specific responses of interest. In the absence of any a priori knowledge of when and where a difference might arise, comprehensive, exploratory analyses may be used that test for amplitude differences across the whole waveform using a "moving window" kind of approach (e.g., tests across successive 50-ms time windows). Such analyses might be run over all electrodes, over regions created by grouping electrodes spatially, or over a targeted region or set of electrodes. In these cases it is absolutely critical that appropriate corrections for multiple comparisons be applied (see Groppe, Urbach, & Kutas, 2011) and that effects be interpreted with caution until they have been replicated.

In other cases, mean amplitudes are measured within an a priori time window of interest and/or in a time window centered on the measured peak latency of a target component or effect. In the latter case, that time window might be determined on the basis of the peak latency in the "grand average" data (i.e., averaged across participants) or calculated independently for individual participants (and there are different issues with each of these approaches). These measures might be made over all electrode sites or in an a priori region of interest. In the former case, it is often informative to include aspects of electrode position as factors in a multivariate analysis, by, for example, organizing electrode positions along dimensions such as front-to-back and left-to-right. This type of distributional analysis can also be used to establish a region of interest for post hoc analyses.

If a reliable amplitude difference between conditions is obtained, one can definitively conclude that the brain is sensitive to the variable that was manipulated (assuming, of course, that one has adequately taken care of confounds and artifacts). Moreover, one can say something about the timing of that difference. The time at which the ERPs can be shown to reliably diverge can be taken as the upper limit on the time that the brain must have appreciated the difference between the two conditions; of course, there could have been earlier differences that were not detectable in the ERP signal. More generally, differences in amplitude on well-studied components may allow more specific inferences, which often take the form of assumptions that a particular cognitive process or neural system is engaged to a greater or lesser degree in one condition than in another. However, it is important to remember that amplitude differences based on averages can arise either because there is a smaller/larger signal on most trials in one condition than in another *or* because there is more temporal variability (*latency jitter*) in one condition than another. If there is more latency jitter in one condition, the response will tend to be distributed over a larger time window, and one will end up with a smaller, broader peak. Of course, there are ways to get around this problem (see, e.g., Puce, Berkovic, Cadusch, & Bladin, 1996)—by examining the variance in peak latency to determine if jitter is a problem, for example—but it is important to be mindful of it. It is also worth noting that there are a number of types of neural changes that could result in a scalp amplitude difference (e.g., smaller postsynaptic potentials in the same set of neurons, activity in a smaller set of neurons, activity that is less temporally synchronous, etc.), which may engender different interpretations.

In addition to amplitude differences and their timing, the latency of well-defined electrophysiological responses can be assessed. This is typically done using peak latency measures, wherein the time of the maximum or minimum value of the waveform in a time window is measured and compared across conditions, often leading to the inference that the "same" neural/cognitive processes are occurring in both but are delayed in one condition relative to another. Care should be taken when measuring peaks: time windows should be chosen that are large enough to encompass the peak of interest in all participants (avoiding the possibility of a spurious maximum or minimum at the boundary of the measurement time window), but small enough to avoid the possibility of measuring a different response, and low-pass filtering is usually desirable to avoid spurious peaks due to noise.

The topography of ERP responses can also be measured and used to make inferences. Rather than looking at voltages through time at an individual location on the head, one can plot the distribution of voltages over the head in a specific window of time. Statistical analyses that include scalp location as factors (e.g., dividing the scalp into regions in the anterior-to-posterior and left/right lateral-to-medial directions) can be used to determine where amplitudes are largest and whether that distribution over the scalp differs across conditions. There is often confusion about what kinds of inferences are licensed when scalp topographic differences are observed. If the brain activity in one condition has a different distribution over the scalp from that in another condition, then it must be the case that the neural source of the activity in the two conditions differs in some way (note that the converse does not hold: different populations of active neurons could add up to produce the same pattern of activity across the scalp). However, it cannot be directly inferred that those sources differ in location, as differences in the strength of (the same set of) underlying sources can also be a cause of topographic differences at the scalp (and normalization cannot compensate for that; see Urbach & Kutas, 2002). Moreover, one cannot make direct inferences about the spatial location of neural sources from scalp topography alone, even at a gross level. For example, a source in the back of the head can create an electrical dipole that has a maximum/minimum picked up by electrode sites positioned over the front of the head (because the closer end of the dipole extends into the neck, where it cannot be picked up) and, similarly, a source in the left hemisphere can create an electrical dipole with a maximum/minimum detected over the right hemisphere (so-called *paradoxical lateralization*; see Van Petten & Luka, 2006). Inferences about neural sources of ERP responses require constraints from other methods and/or mathematical modeling (see discussion in Luck, 2014).

In addition to these standard techniques for analyzing ERP data, there are some newer techniques that are becoming more common and that take advantage of the combined spatial and temporal properties of the signal (these techniques are also increasingly used to help remove artifacts from EEG data; see, e.g., Jung et al., 2000). One example is independent component analysis (ICA); note that here the word "component" refers to a part of the data that is separated mathematically, whereas the term "component" as used more generally in the ERP literature refers to a scalp-recorded effect that is taken to reflect a specific neural or psychological process. ICA treats the observed EEG data as a sum of contributions from a set of fixed, spatially defined sources, and separates the signal into subcomponents by assuming that temporally correlated but spatially separable parts of the signal are coming from separable—independent—sources. The technique makes a number of assumptions, some of which are likely true for EEG data, and others that are almost certainly not (e.g., that the number of sources is the same as the number of sensors). Other spatiotemporal separation techniques, such as principal component analysis (PCA), make different assumptions about the nature of the underlying signal (for a comparison of methods, see Dien, Khoe, & Mangun, 2007). As a general rule, researchers using spatiotemporal analysis techniques should (1) make sure they fully understand the assumptions and limitations of the techniques they are applying; (2) always present raw waveform data as well as the output of these techniques, to allow comparison with the wider literature; and (3) bear in mind that inferences from the output of these techniques require the same process of establishing a *linking hypothesis* (as discussed next) as do inferences from raw waveform features. Indeed, part of what makes using newer analysis techniques difficult is that they require—and currently lack—the kind of extensive replication and validation that is available from decades of work analyzing the raw waveform with traditional approaches.

In sum, because they are direct measures of neural activity, ERPs allow direct inferences about the upper limit of the timing with which the brain appreciates differences between two experimental conditions and, to some extent, the nature of that processing difference (e.g., whether it manifests as a change in amplitude, latency, or scalp topography of the response). Inferences about some aspect of psychology, such as language processing, then require a linking hypothesis: a hypothesis that associates a particular psychological process or state with a particular aspect of the measured response. The quality of the inference drawn depends on the quality of this linking hypothesis, and the hypothesis itself is subject to updating based on new data. The most basic linking hypothesis is that a difference in neural activity means a difference in psychological processing. More specific hypotheses link well-studied aspects of the ERP response (i.e., components) to aspects of psychological processing, including processes that are important for language. In the next section, therefore, we introduce a number of ERP components that have been used to study various aspects of language processing.

KNOWN ERP COMPONENTS USED IN LANGUAGE RESEARCH

In principle, any part of the ERP signal can be informative about the brain's sensitivity to various experimental manipulations, revealing when, how, and how much a given variable influences brain electrical activity. However, having found a reliable effect, it is important to replicate it, and useful for the field to then begin to learn more about that response: What factors modulate it? Which do not? What are the downstream consequences, on other ERP responses or behavior, of this activity? When activity can be reliably elicited and identified and when its functional properties have begun to be well characterized, the field begins to talk about that response as an ERP "component." Despite the fact that we may not fully understand the cognitive or neural bases of each component, accumulated knowledge about ERP components allows researchers to make inferences about the type of processing that is occurring during a particular task. Early use of ERPs was mostly dedicated to developing good linking hypotheses for these components, allowing them to now serve as indices of particular psychological constructs or neural mechanisms. In the following, we highlight some of the well-known, as well as some more newly characterized, ERP components that play an important role in language research. Note, however, that many (perhaps all) of these components are not "language responses" as such, but rather indices of more general processes that are nonetheless informative when used in studies of language. Indeed, language both depends on and influences other cognitive processes, including sensory perception, attention, memory, emotion, reasoning, and decision-making, and behavioral responses of all types. ERPs are sensitive to all of these factors, thereby providing a very rich set of dependent measures.

Language Comprehension

ERPs provide measures that can be obtained without a secondary task, simply while people listen to or view stimuli for comprehension, allowing a picture of language comprehension in its more natural state. However, there are challenges for both visual and auditory studies of language comprehension. In the case of reading, the biggest challenge comes from the fact that, as already discussed, eye movements can create problematic artifacts in ERP data. Therefore, studies with visual words usually present them one at a time in the center of the screen, at a rate of about two to three words per second. Although this rate is slower than eye-movement patterns seen during normal reading, it is important to remember that, different from normal reading, serial visual presentation methods provide no information about sentence length, no preview of upcoming words, and no opportunities to revisit words that have already been read. In fact, when people are allowed to self-select their pace for serial visual presentation, they tend to read at a rate of about two to three words per second (Ditman, Holcomb, & Kuperberg, 2007), suggesting that this is a comfortable speed for the average reader. Furthermore, effects obtained with word-by-word reading often pattern closely with effects seen in natural speech (for example, compare Federmeier & Kutas, 1999, and Federmeier, McLennan, Ochoa, & Kutas, 2002), despite the fact that natural speech unfolds more quickly.

For auditory language comprehension, the major challenge involves time-locking, as it is difficult to pinpoint word onsets (or other points of interest) in continuous speech. Some experimenters insert pauses before critical words in order to have a discrete auditory onset for time-locking (and also then generally make recordings without that critical word, to avoid contamination by co-articulatory information). However, this, of course, reduces the naturalness of the input. More generally, because auditory information accrues over time, even with precise time-locking, ERP responses to auditory language input tend to be more distributed over time (less peaked) than corresponding effects with visual words.

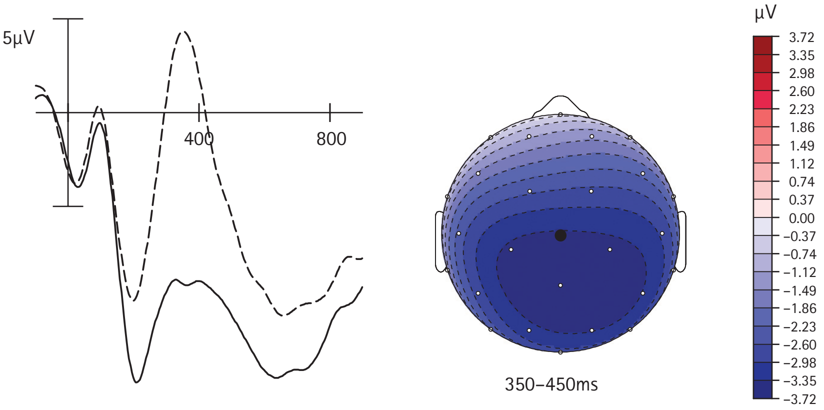
Despite these challenges, ERPs have played a particularly important role in the study of comprehension. Language unfolds very rapidly and on multiple time scales. Some processes, such as the differentiation of consonant sounds, can take place in milliseconds, whereas discourse processing can unfold over the course of minutes. Timing is therefore arguably one of the most important considerations for measures of comprehension; a method like ERPs that can be used across these different time scales is thus very valuable. Moreover, given that processing across different levels of language is interdependent, the continuous nature of ERPs is also advantageous, allowing the simultaneous recording and analysis of a discourse, the sentences that make up the discourse, the words that make up the sentences, and the phonemes or letters that make up the words. As described next, because different subcomponents of language processing have been associated with different ERP components, ERPs provide a means of tapping into specific aspects of processing. Indeed, it is possible to measure multiple subprocesses at once, although experimental designs that focus on a single component are generally easier to interpret.

N400

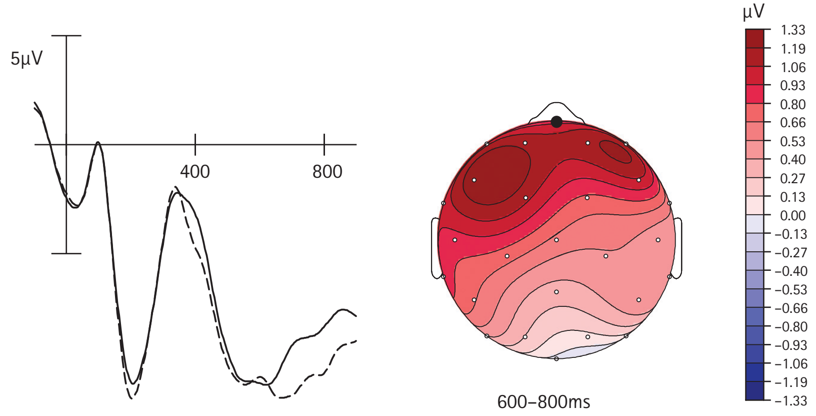
The N400 (Figure 3.1 A) is probably the most widely used ERP measure in language research. It was discovered by researchers looking at the effects of sentential context on word processing (Kutas & Hillyard, 1980a). For example, although the words “dog” and “sugar” have a similar out-of-context (lexical) frequency, when presented as endings to a sentence like “He takes his coffee with milk and . . . ,” the probability of the two words changes. It was expected that the improbable appearance of “dog” in this sentence would elicit a P300 (a component sensitive to probability, as described later). Instead, however, around 400 ms post-word-onset there was a larger negativity to “dog” than to “sugar”—a pattern that is now referred to as an “N400 anomaly effect.” At the same time, words that had an unexpected physical feature (e.g., changed size) did elicit the expected P300, and words that were both semantically anomalous and physically improbable elicited both effects (Kutas & Hillyard, 1980b), highlighting the difference in the brain’s response to these two factors.

Subsequent studies designed to replicate this effect and uncover the neural and functional properties of the N400 have now established that the N400 is not a specific response to semantic anomalies, but rather part of the brain’s normal processing of sensory inputs (see review by Kutas & Federmeier, 2011). In particular, the N400 appears to reflect activity involved in linking sensory stimuli with long-term memory—in other

(A) N400



(B) Frontal Positivity



(C) P600

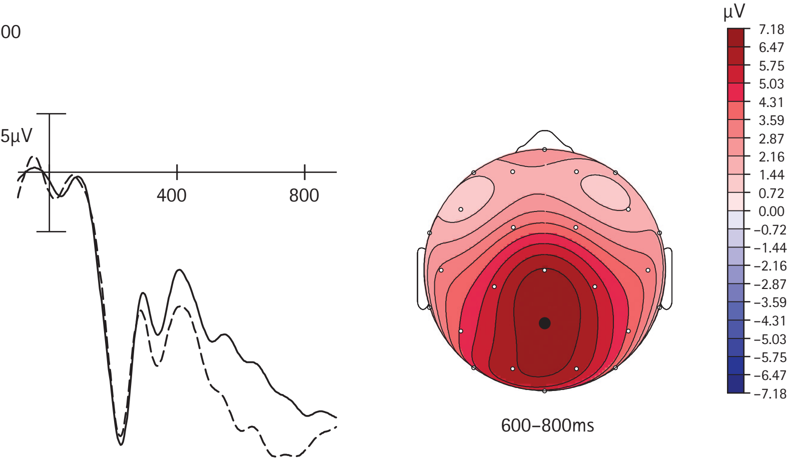


FIGURE 3.1. (A) The N400 effect can be seen in the comparison between sentences with unexpected endings (dashed line), which elicit a large negative peak around 400 ms after stimulus onset, compared to sentences with expected endings (solid line). The topographic map shows the centroparietal distribution of the N400 seen to unexpected endings. (B) A larger frontal positivity can be seen in response to plausible low cloze probability completions of high-constraint sentences (dashed line) compared to the same words completing low-constraint sentences (solid line). The topographic map shows the frontal distribution of the effect. (C) The P600 effect can be seen to syntactically incongruous sentences (dashed line) when compared to syntactically congruous sentences (solid line). The topographic map shows the posterior distribution typical of the P600 effect. In all cases the waveform is taken from the electrode denoted by a solid black circle on the corresponding topographic map.

words, accessing the meaning of those stimuli. N400 activity is observed to words (and word-like strings) in all languages, modalities, and forms (Holcomb & Neville, 1991; Kutas, Neville & Holcomb, 1987), as well as to pictures, scenes, videos, and environmental sounds (Ganis, Kutas & Sereno, 1996; Sitnikova, Kuperberg & Holcomb, 2003; Van Petten, & Rheinfelder, 1995). As such, although the N400 is an ERP component important in the study of language, it is not a *language component* (i.e., it is not specific to linguistic processing).

The N400 manifests as a negative-going component that, in healthy young adults, peaks just before 400 ms after the onset of a stimulus. It has a widespread distribution (when an average mastoid reference is used), which, for written words tends to be largest at centroparietal scalp sites. An important source of scalp-recorded N400 activity seems to come from the temporal lobe, but it is clear that, more generally, the N400 reflects concurrent activity in a highly distributed neural network. A distinguishing characteristic of the N400 is its temporal stability: although participant-level characteristics such as age, language proficiency (e.g., in multilingual speakers), and some neurological or psychiatric conditions may affect N400 latency, within-participant manipulations modulate the size of the N400 but *not* its latency (Federmeier & Laszlo, 2009).

N400 amplitudes are modulated by many factors that affect semantic access. Out of context, N400 amplitudes to words are importantly affected by orthographic neighborhood size, as one of several factors (also including neighbor frequency and number of lexical associates) linked to the size of the lexico-semantic network that a given stimulus normally activates (Laszlo & Federmeier, 2009, 2011; Laszlo & Plaut, 2012). Thus, words with larger neighborhoods elicit larger N400s (i.e., engender more activity in the semantic network). When context information, from individual words (or pictures) or built up across larger language (or nonlinguistic) structures, renders words more predictable, N400 amplitudes are reduced, presumably because some of the information normally associated with that word was preactivated in the course of processing the context. In this sense, N400 amplitudes can sometimes be interpreted as reflecting the "ease" of processing the current word. In sentences, N400 amplitudes are an inverse function of cloze probability (a measure of the percentage of people who would finish a sentence with a particular word), such that words with a high cloze probability elicit a smaller N400 than those with a low cloze probability (Kutas & Hillyard, 1984). The N400 also shows effects of repetition, wherein repeated items elicit a reduced amplitude compared to first presentations (Rugg, Doyle, & Melan, 1993; for a computational account of this, see Laszlo & Armstrong, 2014). These factors, therefore, must be taken into account in experiments in which an N400 is expected.

Because the N400 can be recorded to every word in a list, sentence, or larger language context, and can be measured without the need for an extraneous task (i.e., while participants read or listen for comprehension), studies using the N400 have provided critical insights into a wide range of language-related questions and, in some cases, have challenged ideas and theories that had been built primarily from behavioral data. As just a few examples, N400 data have been important for revealing the role of prediction in language comprehension (Federmeier, 2007), the ability of the RH to comprehend language and differences between the hemisphere's comprehension biases (Federmeier, Wlotko, & Meyer, 2008), and the accrual of word-related knowledge in second-language learners before that knowledge can be tapped into for behavioral responding (McLaughlin, Osterhout, & Kim, 2004).

Frontal Positivity

A well-established property of the N400 is its insensitivity to contextual constraint (Kutas & Hillyard, 1984). That is, although the N400 varies with the cloze probability of the current word in its context, it does not vary as a function of how much a *different* word might have been expected. A low cloze probably word elicits the same size N400 response when embedded in a weakly constraining context (where no single word is particularly expected) as when embedded in a strongly constraining context (i.e., where a different word was highly predicted). The N400 thus reflects the amount of prior activation for the current stimulus, and not something about the global level of prediction or of information accrued across the context. Instead, processing differences associated with disconfirmed predictions manifest in the form of a (pre-)frontal positivity, which follows the N400 (Figure 3.1 B).

For example, Federmeier, Wlotko, De Ochoa-Dewald, and Kutas (2007) observed a frontal positivity in response to low cloze probability completions of high-constraint sentences (e.g., "He bought her a pearl necklace for her *collection*" [expected = "birthday"]) compared to the same words used as completions of low-constraint sentences. This response has now been replicated in a number of studies, and can be distinguished from other positivities to unexpected words (i.e., the Late Positive Complex or P600, as reviewed later in the chapter) both by its frontal (as opposed to posterior) topography and the fact that it is elicited by unexpected words that are, nevertheless, congruent in their contexts (see Van Petten & Luka, 2012, for review). The presence of the frontal positivity can serve as an index of the use of predictive processing mechanisms during comprehension (Wlotko, Federmeier, & Kutas, 2012). In characterizing this effect, however, it is important to contrast two low cloze probability items, rather than examine the difference between an unexpected and an expected item. This avoids difficulties caused by earlier differences on the N400 and also avoids confusing the frontal positivity to the unexpected word with frontal negativity that is sometimes elicited by words of moderate to high cloze probability (see Wlotko & Federmeier, 2012a, 2012b).

P600 and Other Posterior Positivities

Another well-known ERP component used in studies of language processing is the P600 (Figure 3.1 C). The P600 is a positive-going component typically observed between 500 and 1,000 ms after stimulus onset; as is fairly typical of later ERP components, the P600 manifests as a response that usually lasts for several hundred milliseconds and, as such, often has no clear, discrete peak. Unlike the N400, the P600 does not have a characteristic latency; both the amplitude and the latency of this response change, depending on the nature of the experimental manipulation. The distribution also can change (for example, with normal aging the distribution becomes more frontal; Kemmer, Coulson, De Ochoa, & Kutas, 2004), but in young adults it is usually largest over posterior scalp sites.

The P600 is most commonly associated with syntactic anomalies, as it is observed to words that violate the morphosyntactic or phrase structure regularities of language (at least temporarily, as in "garden path" sentences). For example, the P600 was originally described by Osterhout and Holcomb (1992), who gave participants sentences such as "the broker hoped to sell the stock" and "the broker persuaded to sell the stock (was tall)." A P600 was observed to the word "to" in the latter sentence, as participants initially interpreted the word "persuaded" as the main verb of the sentence and therefore expected that a direct object (e.g., the person being persuaded) will follow. However, the P600 is not specific to violations. P600s have also been seen, for instance, to words in object-relative sentences when compared to subject-relative ones, as the latter are easier to understand in English. The P600 can also be "primed," showing a smaller amplitude to words in less preferred sentence structures when these are preceded by a sentence with the same structure (Tooley, Traxler, & Swaab, 2009).

Although the P600 has been most closely linked with syntactic processing, and, on some models, has been specifically associated with efforts to repair and/or reanalyze syntactic information (e.g., Friederici, 1995; Osterhout, Holcomb, & Swinney, 1994) and/or with the difficulty of syntactic integration (e.g., Kaan, Harris, Gibson, & Holcomb, 2000), P600-like responses also have been seen in response to manipulations that, on the surface, seem more related to semantics than to syntax. Kuperberg, Sitnikova, Caplan, and Holcomb (2003) presented participants with three types of critical sentences: the first was a standard, "control" sentence (e.g., "For breakfast the boys would only *eat* toast and jam), whereas the other two types contained semantic/pragmatic violations (e.g., pragmatic violation: "For breakfast the boys would only *bury* toast and jam"; and thematic role violation: "For breakfast, the eggs would only *eat* toast and jam"). Relative to the control sentence, the first type of (pragmatic) violation elicited a larger N400 at the critical word (italicized in the examples). However, the response to the thematic role violation (at "eat" following "eggs") was a large, posterior positivity. Such *semantic P600s* have now been replicated in a range of studies, with varying theories about the type of processing being indexed by the P600 in this case (Brouwer, Fitz, & Hoeks, 2012; Kuperberg, 2007).

P600-like responses (posterior late positivities, which may sometimes also be termed Late Positive Complex, or LPC responses) have also been seen to spelling errors (e.g., Vissers, Chwilla, & Kolk, 2006), leading some to posit that the P600 reflects a general error-monitoring process (Kolk & Chwilla, 2007). Indeed, there are important similarities between the P600 and the more general P300 (specifically, the P3b).

The P3b is a domain-general response that is sensitive to stimulus probability, among other factors. Its latency varies (from around 300 ms to much later) with the time needed to evaluate a stimulus in the context of the task, and its amplitude is sensitive to subjective probability, task relevance, and salience, with larger P3b responses to less probable and more relevant/salient stimuli (see Polich, 2007, for a review). Like the P600, it has a posterior distribution. The P3b has been used in its own right to look at the role of attention and working memory in language processing—for example, in special populations (e.g., Evans, Selinger, & Pollak, 2011). Similarities between the response properties of the P3b and the P600 have raised questions about the language specificity of the P600. Coulson, King, and Kutas (1998), for example, showed that the P600 response was affected by the probability of the grammatical violation. This, coupled with the lack of difference in topographical distribution between the two components, led them to conclude that the components were not distinct. Similarly, Sassenhagen, Schlesewsky, and Bornkessel-Schlesewsky (2014) showed that the P600 aligns in time with response-related processes—again, like the P3b, and arguably against the predictions of many prominent theories of the P600 as a language-related component. Other researchers, however, maintain that the two components are separable, as evidenced by experimental manipulations (e.g., Osterhout, McKinnon, Bersick, & Corey, 1996), studies with clinical populations (Frisch, Kotz, von Cramon, & Friederici, 2003; Hagoort, Wassenaar, & Brown, 2003), and differences in oscillatory signatures (Davidson & Indefrey, 2007; Ford, Roach, Hoffman, & Mathalon, 2008).

Left Anterior Negativity

The left anterior negativity (LAN) is another component that has been linked to syntactic processing (Friederici, 1995; Osterhout & Holcomb, 1992). The distribution and timing of responses labeled as LANs in the literature has been variable, although it is unclear whether this reflects actual malleability of a similar type of brain response or, instead, because different types of brain activity have been (mis)labeled as LANs. The LAN tends to be described as appearing in a similar time window as the N400—between about 300 and 500 ms post-stimulus-onset—but with a more frontal and (sometimes) left-lateralized distribution. The similarity in timing with the N400 (which will be observed to every word) contributes to the difficulty of identifying the LAN, especially since component overlap (e.g., with posterior positivities like the P600/LPC) can shift the apparent distribution of the N400.

The two components have been dissociated experimentally, with an N400 seen to semantic anomalies and a LAN seen to syntactic ones (Münte, Heinze, & Mangun, 1993). Some link the LAN specifically to morphosyntactic agreement (Friederici, 2002). However, there has also been evidence for the component in cases in which the syntactic structure is correct (garden paths: Kaan & Swaab, 2003). Based on this type of evidence, some have argued that the LAN reflects more general, working-memory-related processes, and have associated the more transient LAN responses seen to individual words with sustained negative activity seen for various types of language structures that are working-memory intensive (King & Kutas, 1995; Kluender & Kutas, 1993).

Finally, an "early LAN" (eLAN) has been described in some cases, especially to word-category violations. Friederici (2002) links the eLAN with "first-pass" syntactic processes involved in phrase structure building. However, several recent studies have suggested instead that the eLAN may reflect a domain-general sensory mismatch detection process (similar to the MMN, described later) that registers the difference between the perceptual input and a sensory expectation derived from strong contextual constraints (Dikker, Rabagliati, & Pylkkänen, 2009; Lau, Stroud, Plesch, & Phillips, 2006).

NRef and Other Ambiguity-Related Effects

In addition to frontal negativities that have been linked to syntactic processing and/or working memory, there is a growing literature on negativities that have been linked to the resolution of various kinds of ambiguity. For example, Van Berkum, Brown, and Hagoort (1999) examined the resolution of referential ambiguity, comparing responses to a noun or pronoun (e.g., "the man" or "he") in the context of a discourse that had previously introduced only one possible referent (e.g., "John and Mary . . .") or more than one possible referent (e.g., "John and Bill . . ."). The presence of referential ambiguity elicited a sustained negativity beginning around 200 ms post-stimulus-onset, which had a widespread distribution, but was larger over frontal scalp sites. This difference has been labeled the "NRef effect." Its link to ambiguity-resolution processes is strengthened by the fact that if the referential ambiguity is eliminated prior to the critical noun/pronoun (e.g., because, although two possible referents were originally mentioned, one left the scene before the need to establish reference), the NRef effect is also eliminated (Nieuwland, Otten, & Van Berkum, 2007).

An effect very similar in time course and distribution also has been seen in the context of ambiguity resolution for noun/verb homographs ("duck") presented in syntactically well-specified but semantically neutral contexts (e.g., "John wanted to/the duck . . ."; Lee & Federmeier, 2006, 2009). Again, this effect begins around 200 ms into processing of the homographs and is sustained, even across multiple words (e.g., Lee & Federmeier, 2012). Experiments examining the downstream consequences of this ERP effect (Lee & Federmeier, 2012), as well as its correlation with eye-movement patterns (Stites, Federmeier, & Stine-Morrow, 2013), have suggested that it reflects brain activity associated with suppressing the context-inappropriate meaning of the ambiguous word.

MISMATCH NEGATIVITY

The mismatch negativity (MMN) is seen in response to an auditory change, with or without attention being paid to the stimuli (Näätänen & Michie, 1979). Often in experiments measuring the MMN, participants are exposed to a series of auditory stimuli while they are reading a book, playing a game or are otherwise engaged in a cognitive task. These stimuli consist of "standard" sounds that are mixed with less frequent "deviant" sounds (different from the standards in intensity, pitch, duration, or some other sensory feature). The ERP signal to the deviant sound is characterized by a negative-going deflection around 150–250 ms after the deviance point. The MMN has a fronto-central distribution and has been linked to sources in primary auditory cortex, as well as the inferior frontal gyrus.

Importantly, the MMN is sensitive not only to basic sensory features, but also to abstract patterns, including learned regularities. This makes the MMN a valuable tool for examining speech processing and language acquisition (see review by Pulvermüller & Shtyrov, 2006). MMNs can be recorded even from infants and can be used to assess, for example, the ability to differentiate between phonemes. It is established that in early life infants are capable of differentiating between almost all known phonemes, but that adults only retain the ability to differentiate between those in their native language. With this in mind, Choeur and colleagues (1998) used the MMN to show how memory traces for language information develop. The amplitude of the MMN gets larger in response to a deviant phoneme as the difference between the deviant and the standard becomes greater. Choeur et al. (1998) presented children raised in a Finnish-speaking environment with a standard phoneme from their language mixed with two types of deviants, one that had a different vowel that was a phonemic contrast in Finnish and one with a different vowel that was not a phonemic contrast in Finnish (and which was more acoustically deviant from the standard). At six months of age, children's MMN responses varied with the amount of acoustic difference between the standards and the deviants, independent of phonemic status. However, by one year, the children showed larger MMN responses to the deviant that formed a phonemic contrast in their language, providing neurological evidence for the development of speech memory traces and their emergence between the ages of 6 and 12 months.

LANGUAGE PRODUCTION

Historically, ERPs have been less widely used in studies of language production, in part because it was thought that the motor activity created by overt speech would cause too much contamination of the brain data (although, as discussed in the following, recent studies have actually been successful in collecting clean data even with overt productions). Obtaining enough trials can also be an issue. Many behavioral studies of production have used speech errors as data; however, these errors are generally rare and, in most cases, experimental designs may not elicit a sufficient number of errors to allow traditional analyses of average ERPs. The lack of control over what participants produce in many naming studies can also make it difficult to obtain enough trials of the same type for averaging. Moreover, time-locking to participants' overt utterances is a labor-intensive process (that must be done for each participant individually) and, as in studies of speech comprehension, can be difficult. However, despite these difficulties, ERP experiments in the production domain are becoming more prevalent (e.g., Ganushchak, Christoffels, & Schiller, 2011) and are yielding important insights into the time course and nature of the processes involved in planning speech.

Some research has used overt production paradigms, working to deal with the associated artifacts and other issues, and, in many cases, measuring the same components used in comprehension research. For example, Koester and Schiller (2008) showed Dutch participants words and images that were either morphologically related (e.g., *jaszak* [coat pocket] with an image of a coat [*jas*]), in a semantically transparent or nontransparent way, or were form related but not orthographically related (*jasmijn* [jasmine] with an image of a coat [*jas*]). Participants were asked to read the word aloud, as well as to name the image. N400 responses were attenuated to the morphologically related trails, irrespective of semantic transparency, but not to those trials that were merely form-related. Investigators interpreted this result as evidence that morphological information is distinct from semantic and phonological representations within the mental lexicon. More generally, this study and others like it show that ERPs can be successfully obtained during word-reading and picture-naming tasks, allowing measurement of perceptual, attentional, and language-related components, such as the N400 and the P2 (described next). In other cases, researchers have used clever experimental designs to assess production-related processing without contamination from overt speech (e.g., Van Turennout, Hagoort, & Brown, 1998). As described in more detail in the following, much of this work measures domain-general components, clearly illustrating how the full range of types of brain responses can be harnessed to answer questions about language.

P2

The P2 is part of the visual evoked potential, the normal sequence of electrophysiological responses observed in response to a visual onset, offset, or change. It is a positive-going component that peaks between about 150 and 250 ms. The P2 is sensitive to stimulus features (such as the complexity of a visual stimulus) and is modulated by repetition and attention. In the context of language comprehension, P2 amplitudes have been found to vary with expectancy, as indexed by sentential constraint (e.g., Wlotko & Federmeier, 2007). Recently, P2 response modulations have been observed in the context of simple picture naming with speeded, overt responses. Strijkers, Costa, and Thierry (2010) observed more positive responses to pictures that elicit low-frequency names than those that elicit high-frequency names beginning on the P2 response (around 180 ms). Such effects could be due to visual/conceptual aspects of the picture, but a similar effect was seen in bilinguals for words that are not cognates, compared to those that are. Based on this, and the finding that this effect pattern seems to depend on the intention to name the picture (Strijkers, Holcomb, & Costa, 2011), Strijkers and colleagues have argued that their P2 results index the onset of lexical access occurring around 200 ms into picture processing.

Lateralized Readiness Potential and N200

The lateralized readiness potential (LRP) is a domain-general index of motor-response preparation that has been used to address questions about language production. The LRP is derived, via subtraction, from the readiness potential (RP), and reflects activity primarily from the primary motor cortex (Coles, 1989). To isolate activity specific to the preparation of a particular hand, which generates activity in contralateral cortical areas, the EEG signal obtained from an electrode positioned over the ipsilateral motor cortex is subtracted from that obtained from an electrode over the contralateral motor cortex, thereby removing activity associated with general motor preparation. This component can thus be used to make inferences about whether a particular response is prepared, and, if so, when and to what extent.

One example of how the LRP can be used to answer questions about language makes use of a Go/No-Go task (Van Turennout, Hagoort, & Brown, 1998). In this task two factors are mapped onto response behaviors (which hand to prepare and whether or not to execute a response) in order to provide information about how and when these sources of information become available. Schmitt, Münte, and Kutas (2000) used this paradigm to investigate whether semantic information or phonological information is available earlier in an implicit picture-naming task. They began by mapping the semantic content to the response hand (e.g., respond with the right hand if the stimulus is an animal and the left hand if not) and the phonological content to the Go/No-Go decision (e.g., if the word begins with a vowel, respond, but do not respond if the word begins with a consonant). They then switched this mapping in a second condition, so that semantics was paired with the Go/No-Go task and phonology was mapped to the response hand. An LRP was seen to the No-Go trials when the semantic task was mapped to hand of response but not when the phonology task was, indicating that semantic information must become available before phonological information (i.e., when semantics was mapped to response hand, participants could determine which hand to respond with before being able to determine whether or not to respond, leading to motor preparation, and hence LRP activity, in the No-Go case). This example illustrates how the LRP can be used in any case wherein there is a question about which information becomes available to the response system first.

Another component that can be assessed in these type of designs is the N200 (Schmitt, Münte, & Kutas, 2000), which is generally associated with inhibition. The N200 is a negative-going potential with a fronto-central scalp distribution, which tends to peak between about 200 and 350 ms post-stimulus-onset. The timing of the N200 on No-Go trials (which require response inhibition) can be used to ask questions similar to those assessed with the LRP, but the more peaked N200 may be easier to measure than the slowly ramping LRP (Jansma, Rodriguez-Fornells, Möller, & Münte, 2004). The N200 also has been used to look for evidence of inhibitory processes in the context of bilingual language processing (Rodriguez-Fornells et al., 2005).

Error-Related Negativity

The error-related negativity (ERN, sometimes called the Ne) is a component that indexes errors when people are making a rapid response, and is generally measured as a difference between trials in which an error has been made and those that were answered correctly (Gehring, Coles, Meyer, & Donchin, 1990). The onset of the negative-going fronto-centrally distributed effect is seen just before the behavioral error, and it peaks around 100 ms later when time-locked to the response. The component is thought to have a source in the anterior cingulate cortex, which is an area of the brain associated with cognitive control functions (Dehaene, Posner, & Tucker, 1994). The ERN is often followed by an error-related positivity, and, whereas the ERN is seen to error trials regardless of whether or not the error is noticed, the positivity only follows those trials in which the participant is aware of his or her error (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001).

One use of the ERN in language studies has been to investigate differences in the processing of native versus second languages. For example, Ganushchak and Schiller (2009) showed that native German speakers who were fluent in Dutch as a second language had more interference from their native language, indexed by larger ERNs to errors, when they were carrying out a Dutch phoneme-monitoring task under time pressure. Another study has seen similar differences in bilingual speakers of Spanish and Catalan (Sebastian-Gallés, Rodríguez-Fornells, de Diego-Balaguer, & Díaz, 2006). These studies highlight differences between processing in one's native and second languages that are often not apparent in behavioral studies.

Conclusions

ERPs provide information about when and how processing unfolds in the brain, and, having now been used to gain insights into the cognitive and neurobiological mechanisms of language (and other aspects of cognitive processing) for more than

30 years, they provide a rich set of functionally well-characterized measures. ERPs are sometimes criticized for their relative weakness as a tool for functional localization. However, when used in combination with other methods that have better spatial resolution (e.g., MRI, TMS, optical imaging) or when examined alongside a priori knowledge of component sources (gained from animal studies, clinical studies, source modeling, etc.), ERPs can provide critical information about the brain areas involved in particular types of processing. Moreover, and perhaps especially in complex domains like language, the neural mechanisms of cognitive functions are often less a product of activation in specific brain areas and more about the dynamics of activation across a large-scale brain network. Hence, ERPs are used in clinical populations, not to find out which brain areas are damaged, but to understand how the brain works when damaged (although it is important to note that structural changes to the brain and skull due to damage or medical interventions can significantly change how electrical activity is propagated to the scalp, raising issues for component identification). Moreover, ERPs have been important for revealing how similar brain structures (e.g., the right and left hemispheres) can instantiate importantly different functions via differences in processing dynamics.

In conclusion, ERPs are a method particularly well-suited to the study of language. They provide a continuous measure, and their excellent temporal resolution allows for the assessment of all aspects of linguistic information down to the millisecond level. The lack of need for an overt task allows measures to be taken in a more ecologically valid way, and also allows researchers to extend their work to populations, including infants and some clinical populations, who cannot follow instructions or give behavioral responses. The ability to make measurements without an overt task also means that ERPs can shed light on aspects of processing that cannot be tapped using behavioral methods—for example, revealing evidence for implicit learning of language regularities in participants acquiring a second language (McLaughlin et al., 2004; Tokowicz & MacWhinney, 2005). ERPs can also reveal cases in which similar outcomes are achieved by different underlying processing dynamics, such as shifts away from predictive processing mechanisms in healthy older adults (Federmeier et al., 2002). With continuing advances in our understanding of good methodological practices and of ERP components, it seems clear that electrophysiology will remain an invaluable tool for elucidating linguistic processing for many more years to come.

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CHAPTER 4

STUDYING LANGUAGE WITH FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

STEFAN HEIM AND KARSTEN SPECHT

WHY STUDY LANGUAGE WITH FMRI?

FUNCTIONAL magnetic resonance imaging (fMRI) provides a noninvasive window to the responses of the living human brain under well-defined circumstances. It thus provides an opportunity to study the unimpaired neurobiology of language, instead of relying on inferences from the localization, size, and shape of one or multiple lesions in patient populations. The latter historical approach is certainly powerful. The careful application of symptom-lesion mapping by the forefathers of modern neurolinguistics—Broca, Wernicke, Lichtheim, Déjerine, Geschwind, and others—led not only to the idea that cognitive functions have their own loci in the brain, but even more astonishingly to the notion of a network architecture with nodes and connections (see, in this volume, Blumstein, Chapter 1, and Wilson, Chapter 2). But fMRI, at present the most widely used neuroimaging technique, can do more. It provides insights into the varying degrees to which a region like Broca's area contributes, for example, to varying degrees of syntactic complexity; it permits the quantifiable assessment of the role of contralateral homologue areas despite a lesion in language-sensitive cortex; it represents a wealth of oscillatory bio-signals over time, which can be submitted to elaborate algorithms to detect correlations, causalities, and even predictive coding of upcoming events. An additional advantage is that patients with lesions are rare, whereas university students, the most frequently used "typical healthy subjects," are available in abundance. Recruiting samples from a healthy population also has the advantage that potential nuisance variables can be controlled, stratified, or matched (e.g., age, gender, handedness, IQ, or even prior experience with language experiments).

There are very few limits to the creativity of the fMRI research approach (one being the maximum amount of time participants can spend inside the scanner)—*but there are substantial physical limits to what is possible*. The MRI scanner makes noise that may obscure subtle manipulations in the auditory speech signal. This noise likewise makes it difficult to monitor subjects' vocal responses. The MRI scanner bore is narrow, so visually presented materials have limited extension in space and/or complexity due to typical presentation methods involving projection screens and mirrors. The MRI scanner takes "snapshots" of the brain, so any movement may blur these pictures—and speaking requires and causes head motion.

In this chapter, we dig a bit deeper into these problems and illustrate potential solutions that can be implemented in experimental design. We also discuss technical solutions that have been developed to address these problems from the hardware side. Before doing so, however, it is necessary to understand what it is we do with fMRI. What is the signal we measure? How do we measure it? And why does that cause the various problems outlined in the preceding?

fMRI: BOLD Images for Bold Experiments

As noted earlier, fMRI is a noninvasive neuroimaging technique for investigating functional-structural relationships in the brain. Compared to other methods from the field of neuroscience, fMRI is a relatively new method, and the neuroimaging community recently celebrated the twentieth anniversary of the introduction of fMRI, after the pioneering work in the late 1980s and the early 1990s (Kwong, 2012; Ogawa, Lee, Kay, & Tank, 1990; Turner, 2012). The first decade of fMRI was predominantly marked by methods, developments, and investigations of the neuronal and physiological underpinnings of the BOLD signal (blood oxygenation level dependent). The second decade was characterized by the application of fMRI to study brain functions in healthy participants as well as groups of patients (*brain mapping*). Now in its third decade, fMRI is not only becoming a standard clinical application; the methods also have become sufficiently advanced that fMRI is used for creating network models, investigating dynamic and causal effects within a detected network of brain areas.

The BOLD Signal

When fMRI first appeared on the scene, positron emission tomography (PET) was an established and well-understood tool for functional neuroimaging, although not broadly available and limited in its applicability. Even though the first studies on human fMRI were published in the early 1990s, the idea of using the MRI technique for investigating brain function predates this by many years, as nicely described by two of the pioneers in this field (Kwong, 2012; Turner, 2012). The first fMRI studies were predominantly dedicated to the investigation of the BOLD effect that may in the first instance appear as a "paradoxical" phenomenon: Although neuronal activity is known to consume blood oxygen, increasing neuronal activity is accompanied by regional cerebral blood flow (rCBF) increases such that more oxygenated blood flows into the activated brain area. Since the extraction rate of oxygen (ΔCMR_{O2}) does not increase to the same extent as the blood flow, the relative concentration of oxygenated blood that passes "unused" through an activated area actually increases. Since oxygenated blood (oxy-Hb) is diamagnetic, and deoxygenated blood (deoxy-Hb) is paramagnetic, a change in the ratio of oxy-Hb to deoxy-Hb causes the local magnetic environment to change. This change to the local magnetization (or "susceptibility") can be detected as a differential BOLD signal when a series of appropriate MRI images is acquired.

Underlying the BOLD effect is a multicomponent process that consists of both extravascular and intravascular components, where changes in blood flow, blood volume, and oxygen consumption are the main factors determining the extension and temporal dynamics of the signal (Bandettini, 2009; Buxton, 2012; Duong et al., 2003; Villringer, 2012). However, the exact mechanisms and coupling between the different factors contributing to the BOLD response are still not fully understood. To measure the BOLD signal, one needs an imaging sequence that is both fast and sensitive enough to detect small changes in brain tissue magnetization. Although a range of imaging sequences, including the fast-low-angle-shot (FLASH; Frahm, Merboldt, & Hänicke, 1993; Frahm, Merboldt, Hänicke, Kleinschmidt, & Boecker, 1994; Fransson, Krüger, Merboldt, & Frahm, 1997), are sensitive to BOLD signal fluctuations, today a gradient-echo echo-planar-imaging (EPI) sequence is used almost exclusively (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Bandettini, Wong, Jesmanowicz, Hinks, & Hyde, 1994; Brüning et al., 1995; Kwong, 2012; Turner, 2012). The advantage of EPI is that it can acquire an entire brain slice in less than 100 milliseconds (ms). Hence the entire brain can be covered in less than 3 seconds by conventional MRI systems. An fMRI study that lasts, for example, 15 minutes can easily collect more than 300 whole brain scans. However, EPI sequences are not only sensitive to the BOLD effect, but also to other susceptibility "artifacts" (i.e., signal changes unrelated to brain activity). Consequently, whole-brain fMRI raw data are geometrically distorted to some extent. In addition, there are brain areas that suffer from relative signal loss due to magnetic susceptibility artifacts at borders to air-filled cavities, such as ear canals or above the vocal tract. Because of these artifacts, parts of the inferior temporal gyrus and orbitofrontal cortex typically do not produce reliable fMRI signals. However, a variety of methods have been developed and are now routinely applied to correct the distortions and partially recover the MRI signal in these areas.

Although the physiological mechanisms contributing to the BOLD effect are still not fully understood, the overall time course of the signal is well characterized. Due to its hemodynamic origins, the BOLD signal is a very smooth signal, not properly reflecting the sharpness of neuronal activation. Immediately after the onset of neuronal activation, a small undershoot in the BOLD signal may occur—although more often observed in animal than in human studies—followed by a strong signal increase. The latter reaches its maximum typically 4–6 seconds after the onset of the neuronal activation. Subsequently, the signal decays over a period of 15–20 seconds, including a prominent post-stimulus undershoot, before it returns to baseline (see Figure 4.1 A). Several different mechanisms have been proposed as responsible for this characteristic time course. Although a consideration of the mechanisms is beyond the scope of this chapter, the interested reader is referred to recent papers using biophysical

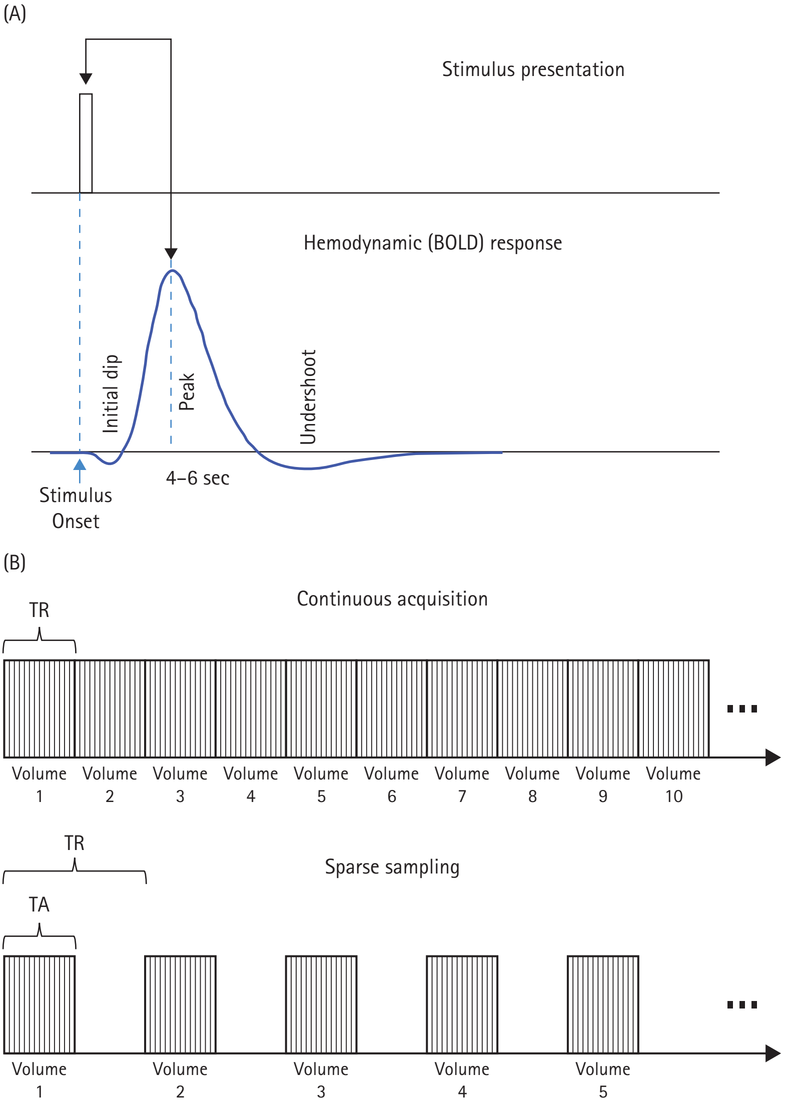
(A)
Stimulus presentation
Hemodynamic (BOLD) response
Initial dip
Peak
Undershoot
4–6 sec
Stimulus Onset
(B)
Continuous acquisition
TR
Volume 1
Volume 2
Volume 3
Volume 4
Volume 5
Volume 6
Volume 7
Volume 8
Volume 9
Volume 10
Sparse sampling
TR
TA
Volume 1
Volume 2
Volume 3
Volume 4
Volume 5

FIGURE 4.1. (A) Schematic display of the BOLD response in relation to the stimulus onset. (B) Two examples of data acquisition schemes, with (top) continuous acquisition, where one volume is immediately followed by the next with no detectable silent gap for the participant, and (bottom) sparse sampling with a silent gap that might be used for stimulus presentation or recording of a verbal response.

Abbreviations: TR = repetition time; TA = acquisition time of one volume.

models (e.g., Buxton, 2012; Buxton, Wong, & Frank, 1998; Hua, Stevens, Huang, Pekar, & van Zijl, 2011).

The recent years have also shown an increasing interest in combining fMRI data with metabolic data, such as rCBF. Until recently, this was accessible only with either a contrast agent–based perfusion MRI or with PET, with the disadvantage of injecting a tracer. With the advent of the arterial-spin labeling (ASL) technique, one is able to perform perfusion measurements within the MR scanner and even within the same session as the fMRI examination (Krieger, Huber, Poser, Turner, & Egan, 2015; Viviani, Messina, & Walter, 2011; Wolf & Detre, 2007). In fact, various options are available, since ASL could be performed as just a single measurement, as a dynamic perfusion examination, similar to BOLD-based fMRI (Hocking, McMahon, & de Zubicaray, 2009a), or as a dynamic supplement to fMRI-based BOLD data with additional information on task-related perfusion changes or during resting state (Viviani et al., 2011). With respect to studies on speech production, it also has been demonstrated that ASL is less susceptible to movement and image artifacts in an overt speech production paradigm than BOLD fMRI (Kemeny, Ye, Birn, & Braun, 2005), making this an interesting option for studying speech production.

Variability and Reliability

Group fMRI studies reflect inter- and intra-individual variability in BOLD signal responses, even in healthy subjects. Some sources of variability under experimenter control can be differences in cardiovascular fitness (affecting the efficiency of blood oxygen uptake/use), and use of caffeine and nicotine. The latter are vasoactive substances, with caffeine in particular being a BOLD signal enhancer (Bartsch, Homola, Biller, Solymosi, & Bendszus, 2006; Honey & Bullmore, 2004). In general, one has to bear in mind that the fMRI signal reflects changes in the ratio of deoxy-Hb to oxy-Hb. This is of special importance in clinical cases, where the cerebrovasculature is typically compromised. Several different methods for assessing the reliability of fMRI have been put forward, ranging from global measures, such as overlap estimates of activations across different occasions (Rombouts et al., 1997; Rombouts, Barkhof, Hoogenraad, Sprenger, & Scheltens, 1998), receiver operating characteristic (ROC) curves (Chen & Small, 2007), to the intra-class correlation coefficient (ICC) (Specht, Willmes, Shah, & Jäncke, 2003). In particular, the ICC has been widely used in assessing test-retest reliability of fMRI for various paradigms and groups of participants (Aron Gluck, & Poldrack, 2006; Fernandez et al., 2003; Hjelmervik, Hausmann, Osnes, Westerhausen, & Specht, 2014; Plichta et al., 2012; Specht, Willmes, et al., 2003; van den Noort, Specht, Rimol, Ersland, & Hugdahl, 2008). In general, the results demonstrate that the highest reliability is achieved by employing paradigms with focused attention, while more passive (i.e., resting) paradigms demonstrate lower reliability. This is of importance for clinical applications where it might be difficult to instruct and motivate patients appropriately and therefore passive paradigms are often used. However, with the advent of "online" analyses on the MR scanner console, quality control is possible, and activation strength/patterns can be monitored during the ongoing fMRI examination (Fernández et al., 2001; Friedman et al., 2008; Specht, Ersland, et al., 2003; Specht, Scheffler, Reinartz, & Reul, 2003).

Experimental Designs

Study Design and Implementation

The presentation of stimuli in an fMRI study is typically controlled by trigger signals from the MR scanner to synchronize them with data acquisition. Most commonly used are block designs or event-related designs. A block design describes an experimental setting with trains of stimuli that belong to the same condition and are presented in succession (e.g., over a period of 30 seconds), alternated with periods of no stimulation or presentation of a control condition, respectively (Matthews & Jezzard, 2004). An event-related design, by contrast, is based on the presentation of single trials of one or more conditions in an arbitrary sequence (Dale, 1999; Rosen, Buckner, & Dale, 1998). Event-related designs often have a lower statistical efficiency than a block design, due to the smaller signal changes generated, but this depends also on the timing of the different trials (Mechelli, Price, Henson, & Friston, 2003). But there are strategies for increasing the efficiency of event-related designs to reliably generate a detectable BOLD signal. One approach to increasing the efficiency of an event-related design with rapid presentation of trials is to use a variable inter-stimulus interval (ISI), called *jittering* (Dale, 1999). In such a design, trials are presented with randomly varied intervals of 2 seconds or more, which causes predictable fluctuations of the BOLD signal that can be modeled in the statistical analysis. This increases the detectability of the BOLD signal as compared to a steady-state situation with a short, but constant, ISI. Ultimately, the selection of an appropriate experimental design depends not only on the research question, but also on whether the task may be simply inappropriate for a block- or event-related design (Matthews & Jezzard, 2004).

The most common fMRI study design employs a method called *cognitive subtraction*. Although it has often been criticized (Friston et al., 1996; Sartori & Umiltà, 2000), it is still the most established and supported method. The core design aspect is to generate two conditions/tasks that differ only in the cognitive component of interest, so that the components of no interest can be "subtracted." It involves the assumption of "pure insertion" (i.e., that each cognitive component evokes its own response and that the measured signal is just a linear sum of the differences). For example, if the goal is to study the brain regions responsible for processing phonetic information, one could create a task condition with phonetic stimuli and another with acoustically matched but nonphonetic stimuli, and so explore the differences between the two—an approach that results in reliable activation within left superior temporal sulcus (Specht, Osnes, & Hugdahl, 2009;

Specht & Reul, 2003). Alternatively, one might also combine a block or event-related design with a parametric modulation (Sternberg, 1969). Here, a stimulus category is factorially varied in one dimension, such as loudness, complexity, or task difficulty. One example that falls under this category is the so-called *sound morphing* paradigm in which a stimulus gradually changes its sound quality so that it "morphs" from white noise into a recognizable speech sound (Osnes, Hugdahl, & Specht, 2011; Specht et al., 2009; Specht, Rimol, Reul, & Hugdahl, 2005).

A pragmatic limitation of fMRI is the duration of a study. Since an experiment needs a certain number of trials per condition to reliably measure the evoked BOLD signal (e.g., 5 blocks of 5 trials per condition for a block design, or 30 trials per condition for an event-related design), one is forced to limit the research questions that should and could be addressed by a single study. Therefore, fMRI studies should be limited to only one or two research questions that could be addressed within one study setup. The main reason for this is that participants become fatigued in this unnatural situation of lying in a scanner and performing cognitive tasks. Consequently, cognitive and task performance at the beginning of the study might be different from that at the end. Another important and often overlooked factor is the instruction given to the participants, as demonstrated in a couple of studies that used manipulated speech-like sounds where specific information about the stimuli were given or not, thus creating different expectancies that can alter the activation pattern (Dufor, Serniclaes, Sprenger-Charolles, & Demonet, 2007; Osnes, Hugdahl, Hjelmervik, & Specht, 2012). Therefore, standardized instructions are a particular prerequisite for limiting the inter-individual variability.

With respect to language studies, especially those with auditory stimuli and/or overt responses, fMRI has additional limitations. The most prominent limitation is the ambient scanner noise that limits audibility of acoustic stimuli. New hardware solutions are under development to provide active noise cancellation during scanning, and it is reasonable to assume that it is just a matter of time until reliable solutions are available. Alternatively, research studies on speech perception can overcome the problem of scanner noise by using a special scanning technique involving inserting brief silent gaps in the data acquisition, also called a *sparse sampling* approach (Hall et al., 1999; Perrachione & Ghosh, 2013; van den Noort et al., 2008) (see Figure 4.1 B). While this has obvious advantages with respect to the audibility of stimuli, it introduces several new limitations. In event-related designs, options for "jittering" of the stimulus presentations are limited, and as one collects a discontinuous time series, analysis approaches that try to fit a hemodynamic response function to the data are inappropriate due to missing time points. In the case of longer silent gaps, one has to optimize the stimulus presentation to hit the peak of the BOLD signal, taking into account the next data acquisition (Perrachione & Ghosh, 2013; van den Noort et al., 2008).

A critical aspect in fMRI design of neurolinguistic studies involves the choice of response modality, since different types of responses, such as a simple button press, overt verbal responses, covert/withheld verbal responses, or passive listening, will add their specific signature to the underlying cognitive processes that are targeted by the study. Examples are given by Indefrey and Levelt (2004) in their meta-analysis of neuroimaging studies of speech production (see, e.g., their Figure 1). Continuous imaging acquisitions involving designs that require an overt verbal response suffer not only in terms of recording during scanner noise, making responses often unintelligible; overt responses also create *massive* magnetic susceptibility-related artifacts in the fMRI images through the movement of the head, the articulators, and the varying volume of the air-filled cavities (Birn, Bandettini, Cox, Jesmanowicz, & Shaker, 1998; Birn, Cox, & Bandettini, 2004). Here, a sparse sampling design is recommended because it ensures that the overt response happens only during the silent gap in imaging (cf. de Zubicaray, Wilson, McMahon, & Muthiah, 2001, Hocking, McMahon, & de Zubicaray, 2009b, for an early implementation; van den Noort et al., 2008; or the seminal paper by Gracco, Tremblay, & Pike, 2005). Processing tools that can correct for deformations of EPI images caused by movements, a so-called *unwarp procedure*, may also help in reducing the extent of those artifacts once the data are acquired (Andersson, Hutton, Ashburner, Turner, & Friston, 2001).

Data Analysis

Once a data set is collected, which might consist of several hundred EPI scans, the data must be processed and analyzed statistically. For this analysis, various software packages are available (e.g., SPM: http://www.fil.ion.ucl.ac.uk/spm; FSL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki; Free Surfer: https://surfer.nmr.mgh.harvard.edu; AFNI: https://afni.nimh.nih.gov; Brain Voyager: www.brainvoyager.com; and LIPSIA: http://www.cbs.mpg.de/institute/software/lipsia). Processing usually starts with a quality check of the data and correction of artifacts. First of all, it must be assured that no obvious imaging artifacts are present in the data, which can occur as "stripes" in the images, distorted or blurred images, and so on. Those artifacts can have many different sources, like technical problems of the MR scanner, sudden and strong movements of the participant, or radio frequency (RF) leakage into the scanner room. Although most artifacts are not able to be corrected and require the data set to be discarded, some can be. Routinely, all data sets are corrected for head movements, since they always occur but should not exceed more than 1–2 millimeters (mm). Other artifacts (e.g., spikes) can be subjected to special tools to reduce their influence (Mazaika, Whitfield, & Cooper, 2005). Processing steps that are especially relevant for group studies are the normalization to a standard reference brain, and Gaussian smoothing of the data to improve signal-to-noise ratio and to reduce persistent anatomical differences between participants and to guarantee a certain amount of smoothness, assumed by, for example, the Gaussian-Random Field theory that estimates corrected *p*-values (Worsley et al., 1996).

From Univariate to Multivariate Analyses

The most common way of analyzing fMRI data is to specify a general linear model (GLM) for each subject's data, where a predicted time course is created that is based on the individual stimulus onset times, stimulus duration, and/or response data. By fitting this hypothesized time course voxel-wise to the fMRI data, one obtains an estimate for each voxel that reflects how well this model fits the real data (Friston, Frith, Frackowiak, & Turner, 1995; Worsley, 1997). Next, these estimates are subjected to analysis at the group level to identify areas that show a significant relationship between predicted and measured time courses across the population.

However, one limitation of this approach is that the analysis is performed for each voxel separately and independently. Thus, the results reflect only differences in activation "strength" on a voxel-by-voxel level. This is a limitation, as task effects might be reflected more in specific activation *patterns*. In contrast, multivariate analysis strategies are more sensitive, as they analyze the entire data space—across voxels and participants. One multivariate method of increasing importance is the independent component analysis (ICA). Here, the entire subject-voxel-time data space can be subjected to the ICA analysis (Beckmann, 2012; Beckmann & Smith, 2005; Calhoun, Liu, & Adali, 2009). An ICA applies higher order statistics to dynamic data and relies on the assumption that the fMRI signal is a linear mixture of hidden sources. However, the *true* number of hidden sources is typically not known and has to be approximated by using algorithms, such as the minimum description length (MDL) (Calhoun, Adali, Pearlson, & Pekar, 2001). The aim of the ICA algorithm is to estimate the mixing matrix, given the number of expected sources within the data set. Hence, the number of expected sources has to be predefined, but no a priori hypotheses about possible spatiotemporal patterns or time courses are required at the initial stage. Further, ICA can be applied on the individual as well as group level, using tensor- or probabilistic-based ICA (Beckmann, 2012; Beckmann & Smith, 2004, 2005) or concatenated spatial ICA (Calhoun, Adali, & Pekar, 2004; Calhoun et al., 2009). The critical selection of relevant components is then based on sorting criteria, using either spatial or temporal criteria. Note that an a priori hypothesis is required for this final step; thus ICA is *not* a hypothesis- or model-free method, as is often claimed. Further, an ICA analysis is often performed in conjunction with a general linear model analysis as a complimentary approach to detect additional effects. For example, an analysis that is based on an ICA is able to separate different, but overlapping networks from each other, like the bilateral network for auditory and phonological processing from that of semantic and syntactic processing (Specht, Huber, Willmes, Shah, & Jäncke, 2008).

Going Meta: Data versus Database

Designing an fMRI study is challenging and rewarding: One has to control all known nuisance variables and manipulate those that help to isolate the linguistic processes of interest. Doing so, it is possible to address very specific research questions with highly specialized designs. The flip side, however, is that one must scan enough participants to have sufficient power to detect meaningful effects. Whereas in the year 2000 a published block-design study could easily involve eight participants (e.g., Burton, Small, & Blumstein, 2000), there is growing consensus that one needs much larger sample sizes that match, or even exceed, those of behavioral studies (Button et al., 2013). Underpowered fMRI studies are likely to produce erratic findings, in particular if a consistency check (e.g., percent of participants showing the group brain activation pattern at the individual level) is missing. Moreover, due to publication pressure, minor results may get published, but fail to replicate. As the meta-analyses of neuroimaging studies of language by Vigneau et al. (2006, 2011) demonstrated, there is hardly a single bit of cortex that has not been activated in at least a handful of papers.

This potentially skewed picture can be addressed in two ways. One option is to run studies with large samples and define the necessary sample size by a priori power analysis. The advantages have been discussed earlier, and the disadvantages are obvious: high expense and a relatively low reward in terms of impact for a study with a long duration that binds resources necessary for other research. The second option is not to acquire data, but rather go to existing databases. Databases can either contain original raw data from published experiments open for use and reanalysis by peers (for neuroimaging data, e.g., OASIS, INDI, or OpenfMRI; cf. Button et al., 2013) or contain reported findings from published studies in terms of peak coordinates and activation statistics per reported contrast (e.g., BrainMap: www.brainmap.org; Neurosynth: http://neurosynth.org). Both options are attractive as complementary ways to increase sample size, signal-to-noise ratio, and thus statistical power in comparison to a single activation study, at negligible expense. Good examples of database studies in the field of language imaging are the meta-analysis of the semantic system by Binder and colleagues (Binder, Desai, Graves, & Conant, 2009) and that of the speech production network by Eickhoff, Heim, Zilles, & Amunts (2009). In the Binder study, 120 original studies were included, yielding data from 1,642 individual volunteers. A potential problem with a meta-analysis of the "semantic system" was that each group of authors might have a slightly different notion of "semantics," so Binder et al. had to define clear inclusion criteria. They were even able to distinguish between "verbal" versus "perceptual" semantics based on the contrasts defined in the original papers. Activation foci reported for these contrasts were then entered into the Activation Likelihood Estimation (ALE) algorithm (Turkeltaub, Eden, Jones, & Zeffiro, 2002) by which the probabilities and extents of activations can be assessed and plotted in an image comparable to that of an original study. By this procedure, individual clusters from individual studies only have a weighted contribution to the overall pattern, which then reflects the relatively consistent involvement of regions in "semantic" tasks.

The validity of this approach was nicely demonstrated by Eickhoff et al. (2009). In their study, ALE was applied to studies listed in the BrainMap data base. Those regions surviving ALE could then be compared to newly acquired original data from their own lab, which provided the advantage that subsequent connectivity analyses could be run on these data. Most important for the purpose of this chapter, there was a convincing match between the original data and the ALE results, representing reassuring support for the application of meta-analyses. Pursuing this approach further, Clos, Amunts, Laird, Fox, & Eickhoff (2013) used the same database to analyze co-activation patterns of left area 44 in Broca's region, finding a stable and functionally heterogeneous parcellation. Such an analysis would scarcely have been possible if all data had to be collected in one lab.

One Region, One Function? Modules versus Networks

Broca's (1861a, 1861b, 1863) finding that a circumscribed damage to the brain resulted in a distinguishable deficit gave rise to the idea of the "siège du langage articulé," the localization of spoken language. Thirteen years later, Wernicke's (1874) report of a different lesion producing different language symptoms extended this idea, which soon led to the notion of a language network in the brain (cf. Lichtheim, 1885): This model architecture featured well-characterized regions in the brain, forming one large functional ensemble.

Subsequent neurological research investigated the functional characterization of different parts of this network, rather than their interaction. The map of Karl Kleist (1934) already had a remarkable precision in this respect, even including functional subdivisions of the cytoarchitectonic areas identified by Korbinian Brodmann (1909)—the more remarkable considering it was based purely on lesion studies. The advent of neuroimaging techniques like PET and fMRI first only continued this tradition, now being able to localize language and other functions in the healthy brain as well as in patients. The Wernicke-Lichtheim idea of a functional network, which had its renaissance in Norman Geschwind's works (e.g., 1970), was rather implicit (see Blumstein, Chapter 1 in this volume).

However, it attracted novel attention with both technical and mathematical advances. The development of diffusion tensor imaging (DTI; see Catani & Forkel, Chapter 9 in this volume), which allowed the investigation of fiber tracts in the living human brain, led to the investigation of the hard-wired connections of the classic language areas (Saur et al., 2008), the anatomical, white-matter based parcellation of Broca's region (Anwander, Tittgemeyer, von Cramon, Friederici, & Knösche, 2007), and the notion of dorsal versus ventral processing streams (Saur et al., 2008) that develop differently during ontogenesis (Brauer, Anwander, & Friederici, 2011; Friederici, Oberecker, & Brauer, 2012). Perhaps even more intriguing was the introduction of algorithms such as Psycho-Physiological Interaction (PPI) in the SPM software package and later Dynamic Causal Modeling (DCM; Friston, Harrison, & Penny, 2003). With these algorithms, novel insights could be gained into the *communication* of brain areas. With PPI, which assesses partial correlations of BOLD time courses in different regions under certain task contexts, Stephan et al. (2003) were able to distinguish a left hemisphere network for letter processing from one in the right hemisphere supporting visuospatial orientation. Most interestingly, the same stimuli were processed by both networks; the left network processed the identity of the letter in a short word, whereas the right network coded its position in the left or right hemifield.

DCM, developed again by the makers of SPM, proved even more powerful: Instead of assessing mere functional connectivity (i.e. the spatiotemporal correlation of the BOLD signal), it allows modeling of "effective" connectivity (i.e., the causal influence that activation in region A exerts over that in regions B, C, D, etc., and vice versa). DCM distinguishes three types of variables: inputs into the network that drive the energy (which can be either sensory or internal, e.g., in a word generation task); the intrinsic connections between regions (which can be uni- or bi-directional and may represent facilitatory or inhibitory influences); and the modulation of their strength by contextual factors such as the presence versus absence of a task, the differential complexity of stimuli, and so on. With DCM, it becomes possible to understand the differential coupling of brain regions (e.g., Eickhoff et al., 2009; Mechelli et al., 2005; Specht, Baumgartner, Stadler, Hugdahl, & Pollmann, 2014), why brain regions are up-regulated under certain conditions (Osnes et al., 2011), or whether different brain regions have different functions in a language task, even in the absence of any BOLD amplitude differences in the classical GLM analysis (e.g., Abel et al., 2011). DCM is based on Bayesian statistics, calculating dependent probabilities of the network parameters given the present set of empirical data. These data are usually BOLD time courses extracted from coordinates, spheres, or anatomically defined regions of interest (ROIs) based on findings in the literature or the preceding GLM analysis. Usually, a set of plausible DCM models is tested in parallel, and Bayesian model selection is used to pick the one model with the best fit. There are various ways to define the model space, which can be done either on the basis of plausibility considerations, in different model "families" each featuring, for example, a unique connectivity pattern but different modulations, or a-theoretically by simply permuting all possible parameters. The current approach is typically limited to a maximum of eight, because each node features a self-inhibitory connection meant to prevent the overall energy in the model from increasing infinitely. Including more than eight regions is theoretically possible, but one buys these additional degrees of freedom with an increasing amount of inhibition in the model, which at some point may simply drain all its energy. These technicalities being explained (and the reader being referred, e.g., to Stephan et al.'s "Ten Simple Rules for Dynamic Causal Modeling," 2010), we will now give some examples of the usefulness of DCM in the realm of language processing.

For instance, Osnes et al. (2011) investigated the hypothesis that the left premotor cortex plays a crucial role in the identification of speech sounds. They morphed auditory music or speech sounds with white noise, thus parametrically varying the amount of music or speech in each auditory stimulus. Participants found performing decisions with respect to whether they heard a "music" or a "speech sound" increasingly easy, but performance at one proportion of signal-to-white noise stuck out: here, participants were already pretty confident about hearing a speech sound when it was in the stimulus, but less confident when they judged the presence of music. Remarkably, it was at that point that the left premotor cortex was involved in, and presumably assisting, speech sound processing. The analysis with DCM now revealed the mechanism underlying this effect. For all auditory stimuli, a network of left Heschl's gyrus, planum temporale, and the superior temporal sulcus (STS) closely interacted. In the presence of auditory speech sounds, however, there was an additional connection from the planum temporale to the premotor cortex, representing the propagation of the signal from the sensory into the motor domain. In addition, the premotor cortex then established a bi-directional connection to the STS for further analysis of the signal.

This example from speech perception illustrates how connectivity analysis adds to the understanding of the functional roles of individual regions within a network when there is already evidence that region A may be involved in process X but not Y. However, connectivity analysis can even reveal latent differences hidden under seemingly comparable activation patterns in different conditions. One example from the domain of spoken language is the study by Abel et al. (2011), who investigated group differences between right-handed, left-handed, or ambidextrous participants during picture naming. In their original analysis of the data, the GLM revealed no group differences whatsoever—a strange and unexpected finding given ample reports of different laterality in left-handers. Therefore, DCM was used in order to test whether laterality differences for handedness could be found in the connectivity patterns, rather than in the amplitude of the BOLD signal. The model space included three models, each featuring posterior (i.e., the left and right fusiform gyrus) and anterior (i.e., area 44 in Broca's region and its right homologue) language regions. The models differed with respect to the nature of the interhemispheric connections, which could be present or absent between the posterior regions, anterior regions, or from posterior to anterior. Bayesian model selection revealed one solution for the entire group of participants, which was replicated for each of the three groups of handedness, implying that the basic underlying connectivity structure was comparable. Most interestingly, however, for the right-handers there was a strong intra-hemispheric coupling in the left hemisphere, whereas a mirrored pattern with additional inclusion of Broca's region was found for the left-handers. These findings again demonstrate the usefulness of connectivity analysis for detecting differences in activation patterns beyond mere variations in BOLD amplitude.

The Resting Brain: Low-Level Baseline or Novel Information?

In the light of the potential problems facing language studies with patients, their number is nonetheless increasing. A closer look reveals that many of these studies do not actually run fMRI tasks, but rather are resting-state studies. In the early PET and fMRI studies, "rest" was used as a low-level baseline condition that could come in the form of null events (i.e., empty trials) or longer blocks with no stimulation or response. Marcus Raichle discovered at one point that the statistical maps for these resting conditions bore surprising resemblances to one another independent of the actual activation task (Raichle et al., 2001). This systematicity was taken to reflect a *default mode* *network* (i.e., the co-activation of regions functionally connected in the brain at rest). Soon, differences in the default mode network were observed for certain disorders, and resting-state connectivity emerged as a novel variable to assess brain networks in the absence of an activation task (Hugdahl, Raichle, Mitra, Specht, 2015).

With resting-state fMRI, one was not limited to investigations of the default mode network. One development involved taking a well-known "language region" previously identified in a classical fMRI language study (e.g., Broca's area) as a seed region and analyzing which other parts of the brain show temporal correlations with the resting-state fMRI time series in it (e.g., Muller & Meyer, 2014). This procedure was termed *seed correlation analysis*. In the Muller and Meyer (2014) study, it revealed a connectivity pattern that nicely resembled activation patterns found in language-task studies. The authors took this overall connectivity pattern as the starting point for subsequent in-depth analyses as to, for example, the cluster structure (identified by ICA) and derived novel insights into the functional nature of Broca's homologue in the right inferior frontal cortex—which might then be verified again with language-task fMRI. The validity of this approach was confirmed by Zhu et al. (2014), who explicitly looked at its reliability.

The advantages of this approach are obvious. One may investigate language-related questions or networks even if the participants cannot perform a task to a sufficient degree inside the magnet. Different groups of participants with distinct language profiles can be compared (e.g., Weiler et al., 2014; Zhang et al., 2014), and therapy-induced effects may be traced (Ferguson, Nielsen, & Anderson, 2014).

Yet, the resting-state approach probably cannot exist without task-related fMRI. The fact that, for example, area 44 is involved in language processing does not mean there is an isomorphism, a one-to-one mapping of structure and function. Meta-analyses have revealed the various functions that area 44 can support (cf. Clos et al., 2013). In addition, task-related connectivity analysis has taught us that the functional interaction of brain regions may vary drastically in different contexts (cf. the DCM studies by Heim, Eickhoff, & Amunts, 2009, vs. Heim, Eickhoff, Ischebeck, et al., 2009). Thus, looking at the resting-state connectivity of a single region does provide insight into the network of other regions it communicates with—at rest. Whether these connections are maintained, how they are intensified or blocked, and whether there is competition or cooperation between connected regions are matters that need to be addressed in well-conducted task-related fMRI studies of language processing, ideally with clear hypotheses and a direct reliance on linguistic theory.

MULTIMODALITY STUDIES

In recent years, fMRI has been combined with other neuroimaging methods, including electroencephalography (EEG) or MR spectroscopy. Simultaneous recording of EEG and fMRI combines the high spatial resolution of fMRI with the high temporal resolution of EEG (see Leckey & Federmeier, Chapter 3 in this volume). Although this is a technically challenging approach, MR-compatible devices and analysis tools are available for performing multimodal integration studies (Debener, Ullsperger, Siegel, & Engel, 2006; Eichele, Calhoun, & Debener, 2009; Eichele et al., 2008; Herrmann & Debener, 2008; Moosmann, Eichele, Nordby, Hugdahl, & Calhoun, 2008; Moosmann et al., 2009; Mullinger, Yan, & Bowtell, 2011).

Functional MRI and MR spectroscopy (MRS) have coexisted as MR applications for many years, but only in recent years have researchers started combining these two sources of information in humans (Falkenberg et al., 2014; Falkenberg, Westerhausen, Specht, & Hugdahl, 2012; Horn et al., 2010; van Wageningen, Jørgensen, Specht, & Hugdahl, 2010; Yücel et al., 2007), despite their application in animal studies for some time (Hyder et al., 2001). Scanners with a field strength of 3 Tesla or above are capable of reliably measuring the concentration of neurotransmitters, like glutamate, which is one of the most important excitatory neurotransmitters in the brain. There is increasing evidence that the regional concentration of glutamate not only is related to inter-individual behavioral differences, but also may influence the fMRI signal in remote brain areas (Falkenberg et al., 2012; Falkenberg et al., 2014; van Wageningen et al., 2010). To assess the concentration of the most important inhibitory neurotransmitter, namely gamma-aminobutyric acid (GABA), one needs a special sequence, like MEGA-PRESS (Henry, Lauriat, Shanahan, Renshaw, & Jensen, 2011). GABA is of particular interest, since inhibitory mechanisms are related to many central functions, and its influence on the BOLD signal has been recently demonstrated (Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009; Muthukumaraswamy, Evans, Edden, Wise, & Singh, 2012).

Conclusion

Neuroimaging techniques such as fMRI have expanded our insight into the complex neuronal architecture and mechanics by which language is processed in brain regions that form networks. Still, many technological issues need to be solved before we reach spatial and temporal resolutions sufficient to allow modeling of the neuronal interactions supporting speech and language use, or develop protective and therapeutic strategies for more efficient recovery from language-relevant brain damage.

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CHAPTER 5

TRANSCRANIAL MAGNETIC STIMULATION TO STUDY THE NEURAL NETWORK ACCOUNT OF LANGUAGE

TERESA SCHUHMANN

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is based on the physical principles of mutual and electromagnetic induction. These refer, respectively, to the physical phenomenon that electrical and magnetic fields can be reciprocally converted, and the possibility that a current can be produced in a conductive medium by either moving the conductive object through a static magnetic field, or by placing the conductive object into a time-varying magnetic field (Faraday's law). Based on these two principles, with TMS one is able to noninvasively induce a secondary current in the brain, acting as the conductive medium, by applying a time-varying magnetic field using an electromagnetic coil. The beginning of modern TMS was the development of the first TMS device by Barker in 1985 (Barker, Jalinous, & Freeston, 1985). By stimulating the human motor cortex and inducing the respective motor contractions, Barker and colleagues measured the connectivity and excitability of the motor cortex in healthy participants. Moreover, Barker performed the first clinical examinations by comparing conduction times of motor responses in healthy participants and patients with different neurological diseases (Barker, Freeston, Jabinous, & Jarratt, 1986; Barker, Jalinous, & Freeston, 1985). Subsequently, Pascual-Leone and colleagues (Pascual-Leone, Gates, & Dhuna, 1991) were the first to study language with TMS.

Basic Principles of TMS

Transcranial magnetic stimulation is based on the aforementioned principles of electromagnetic induction. A large and brief pulse of current is discharged into an electromagnetic coil held above a participant's head. This current produces a time-varying magnetic field perpendicular to the current, lasting for approximately 100–200 microseconds (μs). The magnetic field passes transcranially through the intact skull into the tissue and induces a perpendicular electric field. The strength of the induced electric field mainly depends on the rate of change of the magnetic field. Due to the electrical conductivity of the living tissue, the electric field leads to an electrical current in the cortex parallel but opposite in direction to the current in the coil (Lenz's law), and subsequently to a depolarization of the underlying neurons (Hallett, 2000).

Physically, the rate of change of the electric current in the coil determines the strength of the induced electrical field. Therefore, the electrical field has its maximum at the instant of the switching of the electrical current since this point marks the maximum rate of change of the current. With increasing current strength, this rate of change decreases, and consequently the induced electrical field strength decreases, reaching zero at the current's maximum value.

TMS Hardware

Any TMS device consists of a bank of capacitors capable of producing high discharge currents, and an electromagnetic stimulating coil to apply magnetic pulses of up to 4 Tesla. The high and rapidly changing currents are discharged into the coil, thereby creating a strong and time-varying magnetic field (pulse) that can reach its peak in less than 250 μs. This time-varying magnetic field induces an electric current in the neuronal tissue underneath the coil, and thus induces action potentials when applied at proper intensities. Different geometric shapes of the electromagnetic coils allow for different stimulation characteristics, including focality, depth of penetration, and strength of the induced activity changes. For example, in the so-called circular coil, low-resistance copper is wound in one or several turns into a ring-shaped configuration. This coil type generally has no single magnetic field focus but a maximum current in the entire outer winding, forming a ring-shaped magnetic field around the coil. Therefore, the site of stimulation in a standard circular coil is not well defined. Inside a figure-of-eight coil there are two ring-shaped coils, mounted next to each other and coated by the characteristic butterfly-shaped coil mantle. Importantly, the current inside each of these two coil windings circulates in opposite directions, causing the two respective magnetic fields of these two coil loops to summate at the coils' intersection. This enables a more focal magnetic brain stimulation as compared to other coil geometries, making it, generally speaking, more suitable for research in cognitive neuroscience (e.g., in the context of functional mapping of the brain or identifying causal brain-behavior relationships).

Chronometric versus Repetitive TMS

TMS can be applied with one pulse at a time (*single-pulse TMS*), in pairs of pulses separated by a variable interval (*paired-pulse TMS*), or in multiple pairs of pulses (ranging from *triple-pulse* up to *quintuple-pulse TMS*). Importantly, all of these ways of application are usually linked to the onset of an external event such as task onset, and therefore are capable of revealing information about the chronometry of a cognitive process. We thus can refer to these approaches as chronometric or event-related TMS, or in other words, protocols that are used to study causal chronometry in brain-behavior relations.

In contrast, TMS can also be applied in a repetitive manner (repetitive (r)TMS). Today, we distinguish between conventional and patterned protocols of repetitive stimulation (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). In conventional protocols, single TMS pulses are repeated and applied in a regular rhythm. Here, one can once again make a distinction between low-frequency rTMS (stimulation frequency of 1 Hz or less) and high-frequency rTMS (stimulation frequency of more than 1 Hz). With newly developed TMS stimulators, the maximum stimulation frequency that can be reached lies at 250 Hz. Patterned rTMS refers to repetitive application of short rTMS bursts at a high inner frequency, interleaved by short pauses of no stimulation. In recent years, a new protocol was introduced called theta burst stimulation (TBS). In TBS protocols, short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS) or intermittent (iTBS) train (Di Lazzaro, 2008; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

The important feature of both conventional and patterned TMS is that it is capable of modulating the excitability of the stimulated area even beyond the duration of the TMS application itself. The after-effects of TBS were found to be significantly longer lasting compared to conventional rTMS (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) with shorter stimulation time needed. Therefore, patterned rTMS protocols are starting to play a larger role in brain stimulation. Both 1 Hz rTMS and cTBS are consistently found to produce lasting inhibitory after-effects. High-frequency rTMS and iTBS, on the other hand, induced lasting facilitatory after-effects on motor corticospinal output in healthy participants. In sum, the number of repetitive stimuli per second, the stimulation frequency, as well as the stimulus intensity, the duration of the stimulation train, the inter-train interval, and finally the total number of trains and total number of stimuli represent the stimulation parameters of TMS, which may all be combined in different ways to produce the desired neuronal effects at the targeted brain site.

TMS can thus be applied in a chronometric, event-related manner, as well as in a repetitive manner. Both options provide excellent tools for the study of cognition. Applying TMS in a chronometric manner, appropriately delivered in time and space, can disturb the function of a cognitive process online. Applying TMS repetitively results in an offline, and longer lasting effect. Those two effects enable the study of two aspects of the contribution of a given cortical region to a specific behavior: What does it do? And when does it do it?

Critical Issues of TMS in Language Research

Pioneers in the stimulation of language-related areas were not cognitive neuroscientists, but neurosurgeons, namely Wilder Penfield and George Ojemann. They used direct cortical stimulation in awake neurosurgical patients to probe language processing (Ojemann, 1979; Penfield & Jasper, 1954; see Duffau, Chapter 8 in this volume). Ojemann was able to show that applying a direct current to a focal brain region can selectively disrupt linguistic processes. As exciting as these findings were, the invasive nature of Ojemann's research did not allow for extensive testing of language functions in healthy individuals. The introduction of TMS led to new possibilities as it indisputably represents a unique research tool within the spectrum of techniques used to investigate how the human brain works and how neural mechanisms relate to behavior and cognition. TMS allows researchers to noninvasively induce local neural activity changes in the healthy human brain. It thereby directly probes the behavioral and cognitive consequences of these experimentally induced neural perturbations under controlled experimental and repeatable conditions.

Nevertheless, TMS also faces general challenges, as well as challenges that are specific to its application in the domain of language. Advances in technological developments of TMS, as well as TMS protocols and designs, have been able to address some of these challenges. Yet, several problems inherent to the method and rationale of TMS, as well as the neuroanatomy of language, still pose critical limitations. It is important to be aware of these limitations when conducting or interpreting TMS language studies.

First, and most important, the neural correlates of language include a widely distributed cortical circuitry of which several regions are not easily identifiable or reachable by TMS. The challenges thus already start with the crucial question of optimal TMS coil placement, or how to best determine the optimal stimulation site. In fact, knowing exactly where and how to place the TMS coil has been shown to be decisive for inducing the intended neural and behavioral consequences (Sack et al., 2009). Yet, in practice this crucial starting point of any TMS investigation often lacks clear criteria of which exact "hot spot" within a given brain region should be targeted. Moreover, determining such an exact "hot spot" would require the availability of individual anatomical or functional brain imaging data, depending on whether the intended stimulation target site has to be anatomically or functionally defined on each individual brain reconstruction. Often, such individual brain-imaging data are not available, and consequently alternative coil-placement strategies are employed, using, for example, anatomical landmarks on the scalp or the 10–20 electroencephalography (EEG) system to place the TMS coil. This falsely assumes a perfect and consistent correspondence between anatomical scalp landmarks and the underlying neural structures across participants.

What further complicates the matter is the fact that even a perfect coil placement above the exact "hot spot," for example as determined by preceding functional imaging measurements, still leaves the question of how to best rotate the TMS coil. It has been shown that even when stimulating the exact same stimulation site, rotating the coil such that the induced electric field crosses the targeted neural structures in either a parallel or perpendicular configuration clearly affects the outcome of the stimulation. While it has been suggested that a perpendicular crossing of the target gyrus might be most effective in the visual cortex (Kammer, Beck, Erb, & Grodd, 2001), it remains largely unclear what rotation of the coil is optimal for any other brain region or experimental question.

Beside coil placement and rotation, the largest factual limitations of TMS are its very limited depth of penetration and its rather limited spatial resolution. While both parameters depend on TMS coil geometry and coil size, it must be realized that the magnetic field strength of the TMS coil decreases logarithmically with increasing distance, limiting its direct effectiveness to a few centimeters (cm) from the coil. It thus must be stated very clearly that TMS is limited to the superficial areas of the cortex with a maximum distance of approximately 2–3 cm from the coil on the scalp (Sandrini, Umilta, & Rusconi, 2011; Thielscher & Kammer, 2004; Weyh, Wendicke, Mentschel, Zantow, & Siebner, 2005). Consequently, it is not possible to directly stimulate any deeper-lying brain structures with TMS. Since several language-related areas are located in the depth of the Sylvian fissure, direct stimulation effects of these areas are questionable. However, the penetration depth is sufficient to effectively stimulate the fronto-parieto-temporal language areas at the cortical surface.

The focality of the magnetic field distribution also decreases with increasing distance, limiting the spatial resolution of TMS to roughly 1–2 cm, depending on the geometry and size of the TMS coil used, as well as the distance from the coil. In addition, language-related areas often lack a clear region-specific separation in space, as is the case in other cognitive functions such as memory or attention, which again makes selective targeting of these regions with TMS problematic. Finally, language, as one of the most complex cognitive skills, is almost never exclusively processed within single isolated brain regions, but requires the organized neural activity within widely distributed and dynamically interacting neural networks. It is therefore often difficult to attribute a behavioral effect following the stimulation of a single area to changes in the entire network.

What complicates the matter is the fact that a real validation of TMS-induced neural effects is usually not possible in classical behavioral TMS studies. Here, the circular assumption often is made that a successful TMS-induced behavioral change is indicative of a successful neural efficiency of the used TMS protocol at the site of stimulation. However, such behavioral changes are potentially confounded by many psychological (e.g., placebo) or indirect (e.g., remote network effects, sensory side effects of stimulation, etc.) effects of TMS. This general limitation of TMS, namely interpreting a behavioral effect of stimulation as a validation of successful neural efficiency of TMS, represents an invalid circular argument. This is particularly critical in studies where the intended stimulation site is physically at the border or outside the reach of the induced magnetic field of TMS, as often is the case in language studies.

In directly addressing this critical question of neural versus behavioral effects of TMS, few studies have been able to apply TMS while simultaneously measuring the neural and metabolic consequences using concurrent functional imaging techniques such as EEG, positron emission tomography (PET), or functional magnetic resonance imaging (fMRI) (for an exhaustive review, see Reithler, Peters, & Sack, 2011). These studies have consistently revealed that locally applied TMS has both local *and* remote neural network effects. This means that the TMS-induced local neural activity changes are not restricted to the directly targeted brain region, but rather spread along anatomical and functional connections to widely distributed remote regions within a specific neural network. Interestingly, these remote effects are state-dependent, indicating that TMS specifically co-activates those remote regions of a given network that are functionally relevant during cognitive performances. It has been shown that these remote network effects of TMS are also functionally relevant for successful performance of the task under investigation. This may seem to be a limitation of TMS, as it complicates the simple brain-behavior relationship studies in classical behavioral TMS experiments. However, this also represents a great advantage of TMS, as TMS not only affects single isolated brain regions, but dynamically interacts with widely distributed brain networks. It thereby indirectly opens the door to deeper-lying brain regions outside the reach of direct stimulation and in that way allows the possibility of studying the functional relevance of distributed neural networks for behavior and cognition.

Apart from the technical limitations of TMS, researchers often experience more practical issues during the application of TMS in language studies. For example, TMS causes strong side effects, such as muscle twitches, when inferior frontal areas are stimulated. In language-production studies, this is problematic, since participants are occasionally unable to speak correctly as a consequence of the muscle stimulation. Moreover, in online TMS studies, the clicking sound of the TMS coil can be disturbing and interfering with auditory stimulus presentation. Finally, when participants have to complete a task in which a vocal reaction is required, the standard setup, in which the participant is often resting her head in a chin rest with the TMS coil being attached to a TMS coil holder, cannot be used, as in this setup movements of the mouth are not possible. Therefore, the coil and the participant's head ideally are handheld during online task performance (see Figure 5.1).

Despite these serious challenges in using TMS to study such a complex cognitive ability as language, several well-conducted studies have successfully demonstrated the value of

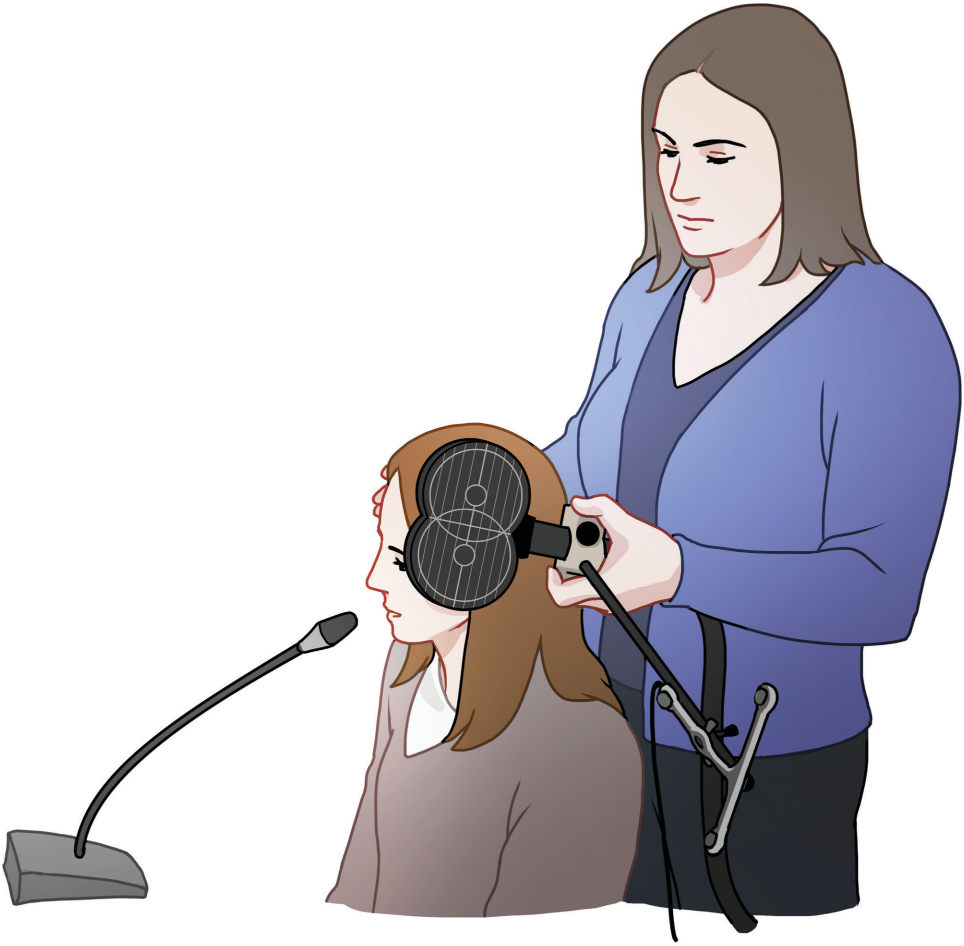

FIGURE 5.1. Optimal coil placement setup during online speech production experiments. The participant's chins is not placed in a chin rest so that he or she can freely move his or her mouth. Therefore, the stimulation coil has to be handheld.

Figure courtesy of Minye Zhan.

TMS in investigating the functional relationship between a given set of brain regions and various aspects of language processing. Today, over 25 years after the publication of the first pioneering study on TMS and language by Pascual-Leone and colleagues (1991), it is safe to conclude that TMS has been demonstrated to be a valuable tool to study the neural network account of language. Following the described logic and capability of different TMS protocols, three levels of investigations using TMS to study language will be distinguished in this chapter, demonstrating that TMS is able to (1) test the functional relevance of brain regions for language processing, (2) chart the exact time period of functional relevance of these regions for successful language processing, and (3) unravel the dynamics within distributed neural networks underlying language processing.

Using TMS to Test and Segregate the Functional Relevance of a Brain Region for Language Processing

Pascual-Leone and colleagues (Pascual-Leone, Gates, & Dhuna, 1991) were the first to study language with TMS. They induced speech arrest in pre-surgical epilepsy patients in order to determine whether TMS could be used as a noninvasive alternative to intracarotid amorbarbital testing. Speech arrest is an effect that is obtained when rTMS is applied to the left inferior frontal gyrus. Participants undergoing such stimulation experience everything ranging from a mild hesitation to say something up to complete mutism. One of the patients of Pascual-Leone and colleagues noted, "I could move my mouth and I knew what I wanted to say, but I could not get the numbers to my mouth" (Pascual-Leone et al., 1991, p. 699).

It has been shown that frequencies as low as 4 Hz are sufficient to induce a speech arrest when using a stimulation intensity of 140% of the resting motor threshold or higher (Epstein et al., 1996). Higher frequencies can lead to prominent facial and laryngeal muscle contractions, and can significantly increase the discomfort or pain associated with stimulation, making speech arrest more difficult to determine. Other research groups were also able to show that rTMS can produce transient speech arrests (Epstein, 1999; Epstein et al., 1996; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994; Michelucci et al., 1994). Epstein and colleagues (1999) revealed that rTMS to the left inferior frontal area led to an arrest of spontaneous speech and reading aloud, while other forms of language processing, such as writing, comprehension, singing, and so on, remained unaffected.

Following these pioneering findings, several studies have aimed at using TMS in order to bring to light the functional role of the left inferior frontal gyrus (IFG), Broca's area, during language processing and production (Andoh et al., 2006; Devlin, Matthews, & Rushworth, 2003; Flitman et al., 1998; Hartwigsen, Siebner, Deuschl, Jansen, & Ulmer, 2010; Kohler, Paus, Buckner, & Milner, 2004; Mottaghy et al., 1999; Mottaghy, Sparing, & Topper, 2006; Naeser et al., 2005; Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004; Pobric, Jefferies, & Ralph, 2007; Romero, Walsh, & Papagno, 2006; Sakai, Noguchi, Takeuchi, & Watanabe, 2002; Shapiro, Pascual-Leone, Mottaghy, Gangitano, & Caramazza, 2001). We have seen from functional brain-imaging studies that within the left IFG, there seems to be an anterior-posterior division of labor for semantic and phonological processing (Buckner, Raichle, & Petersen, 1995; Fiez, 1997). TMS studies have been able to support this claim and have confirmed this division of labor, while further clarifying the specific regional contributions to semantic and phonological processing. Devlin and colleagues (2003), for example, were interested in the role of the left inferior prefrontal cortex (LIPC) in phonological processing. In their fMRI study, they demonstrated that both semantic and phonological processing activated a common set of areas within this region. In a following TMS experiment, they stimulated the anterior portion of the LIPC to determine whether this region was essential for normal semantic performance. Both repetitive and single-pulse TMS significantly slowed participants' reactions for the semantic but not for the perceptual control task. They thus demonstrated that the anterior and posterior regions of the LIPC contribute to both semantic and phonological processing, although to different extents.

Likewise, Kohler and colleagues (2004) stimulated anterior left IFG with fMRI-guided rTMS and showed that semantic decisions were slower after stimulation, which again shows that anterior left IFG is necessary for semantic processing. Nixon and colleagues (2004) examined the role of the left IFG in phonological processing and verbal working memory. They applied rTMS to the posterior left IFG while participants performed a delayed phonological matching task. They then compared the effects of disrupting this area either during the delay, or memory, phase or at the response, or decision, phase of the task. When the stimulation was applied during the memory phase when participants were required to remember the sound of a visually presented word, rTMS impaired their accuracy. When delivered later in the trial, during the decision phase, rTMS had no effect. They therefore concluded that the posterior region of the IFG is necessary for the normal operation of phonologically based working memory mechanisms. Similarly, Aziz-Zadeh and colleagues (Aziz-Zadeh, Cattaneo, Rochat, & Rizzolatti, 2005) were interested in whether blocking internal speech can be achieved by rTMS and included a phonological task in their study. They found that rTMS over posterior left IFG leads to higher reaction times compared to trials in which no stimulation was applied. This study again supported the role of posterior left IFG in phonological processing. Taken together these TMS studies significantly broaden the previous neuroimaging results by demonstrating that anterior left IFG is necessary for semantic processing, while posterior left IFG is necessary for phonological processing (Devlin & Watkins, 2007), as suggested by earlier functional imaging studies (Costafreda et al., 2006; Vigneau et al., 2006). Other studies showed that not only the left IFG but also the inferior parietal cortex (IP) contributes to phonological processing (Kirschen, Davis-Ratner, Jerde, Schraedley-Desmond, & Desmond, 2006; Pattamadilok, Knierim, Kawabata Duncan, & Devlin, 2010; Romero et al., 2006; Stoeckel, Gough, Watkins, & Devlin, 2009).

The left posterior superior temporal gyrus (PSTG), Wernicke's area, has also been targeted by TMS (Andoh et al., 2006; Mottaghy et al., 1999; Mottaghy et al., 2006) in order to unravel its functional contribution to language processing in healthy human volunteers. Andoh and colleagues (2006) explored the role of the left PSTG in semantic and phonological processing with fMRI-guided rTMS. While listening to sentences in their native language and in languages unknown to them, they were required to perform a fragment-detection task, during which they also received rTMS. Low-frequency rTMS applied over Wernicke's area resulted in a decreased reaction-time response and was stronger for native than non-native languages. This facilitatory effect was specific to stimulation of Wernicke's area. The authors therefore concluded that the left PSTG is involved in lexical processing. Other studies have also reported facilitatory effects of rTMS on language areas (Mottaghy et al., 1999; Mottaghy et al., 2006; Wassermann et al., 1999). In these studies, rTMS to Wernicke's area influenced picture-naming latencies, resulting in a shortening of naming latencies without affecting the accuracy of the response; rTMS over the visual cortex, Broca's area, or over the corresponding sites in the nondominant hemisphere had no effect. Repetitive transcranial magnetic stimulation over Wernicke's area also led to a brief facilitation of picture naming, possibly by shortening linguistic processing time.

Finally, using the approach of employing TMS to test and segregate the functional relevance of a brain region for language processing, the role of primary and secondary motor cortex in speech (Aglioti & Pazzaglia, 2010; Aziz-Zadeh et al., 2005; Cattaneo, Devlin, Salvini, Vecchi, & Silvanto, 2010; Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Mottonen & Watkins, 2009; Tremblay & Gracco, 2009; Watkins & Paus, 2004; Watkins, Strafella, & Paus, 2003) has also been successfully shown (for a complete overview, see Cattaneo, 2013; Devlin & Watkins, 2007; Hartwigsen, 2015). In sum, these studies show how TMS can probe the functional relevance of a given language-related brain region for a particular language process. In particular, the demonstrated ability of this approach to segregate functionally distinct anatomical subregions and a respective double-dissociation with distinct subfunctions is highly valuable.

Using TMS to Chart the Exact Time Period of Functional Relevance of Single Brain Regions for Successful Language Processing

TMS is not only able to give information about the functional relevance of a brain region, but it can also provide information about *when* this area is needed for successful task execution. One can thus chart the exact time period of functional relevance for successful language processing in a brain region. To do so online, event-related protocols are used, during which trains of pulses are given at different points in time. Töpper and colleagues (Töpper, Mottaghy, Brugmann, Noth, & Huber, 1998) belong to the pioneers in chronometric TMS designs in language research. They were interested in the role of Wernicke's area and the motor cortex during picture naming and applied single TMS pulses to these areas at different points in time, ranging from 5,000 milliseconds (ms) before picture presentation up to 300 ms after picture presentation. Interestingly, they did not find an effect on naming accuracy by TMS over any of the stimulated areas, or any effects of motor cortex stimulation on naming latencies. However, single-pulse TMS over Wernicke's area resulted in a reduction in reaction times when the pulses were given 1,000 ms and 500 ms before picture presentation. The authors concluded that TMS is able to facilitate lexical processes due to a general pre-activation of language-related neuronal networks when delivered over Wernicke's area.

Schuhmann, Schiller, Goebel, and Sack (2009) also performed a study to investigate the temporal dynamics of the posterior IFG in picture naming. In their study, participants were shown pictures of monosyllabic nouns and asked to name them aloud. Using an online event-related triple-pulse MRI-guided TMS paradigm, these authors applied real and sham TMS to Broca's area at various time points between 150 and 575 ms following picture presentation. They observed that vocal reaction times were significantly slowed down when real TMS pulses were delivered around 300 ms after picture presentation, but not when TMS pulses were applied earlier or later in time. The authors concluded that Broca's area was functionally relevant at 300 ms after picture presentation and could successfully link this neural timing information to the model of speech production presented by Indefrey and Levelt (2004). They interpreted the slowing down of the vocal reaction-time data as a disruption of the syllabification process through TMS. Syllabification is defined by Indefrey and Levelt as an abstract segmental representation that takes place prior to the activation of articulatory motor representations that are required for speech output, and occurs at around 330 ms after the presentation of a picture, according to their neurolinguistic model.

Following up on this study, Wheat and colleagues (2013) used fMRI-guided chronometric TMS to investigate whether the effects that were found during picture naming when stimulating Broca's area can also be seen when reading words. They delivered pulses to individually predefined functional maps in the left IFG 70–500 ms after stimulus onset. They found that both reading and picture-naming reaction times were significantly slower when TMS pulses were applied to Broca's area at 225–300 ms. This study replicated the findings reported by Schuhmann and colleagues (2009) and expanded the revealed functional chronometry of Broca's area for picture naming to reading.

To conclude, these studies clearly demonstrate the feasiblity of using event-related chronometric TMS protocols in the domain of language research. These approaches are of great potential value, as they allow charting the exact time point at which certain language-related brain regions are functionally needed for successfully performing specific language (sub)processes. Considering the complexity of the language network and the highly distributed neural processing underlying the various subfunctions of language, it seems necessary, however, to apply short event-related TMS pulse bursts consisting of three or more high-frequency pulses time-locked to the onset of the task, and temporally separated by an appropriate inter-trial interval to avoid carryover effects, as has successfully been done in some studies (Schuhmann et al., 2009; Wheat et al., 2013).

From Single Brain Regions to Unraveling the Dynamics of the Neural Network Account of Language

So far, we have discussed how TMS can be used to test and segregate the functional relevance of a brain region and how the exact time point of functional relevance of single brain regions can be charted for successful language processing. However, recently, language studies have started to look at the neural network accounts of language. These studies not only looked at one brain region at a time, but also looked at various brain regions together. This can be done by stimulating various brain regions separately, receiving timing information of each of the regions, and thereby receiving indirect evidence about information flow. However, stimulating two or more areas simultaneously is also possible. Thereby, inter-hemispheric interaction and compensation can be studied, if they are compared to unifocal stimulation. Another very elegant and recent approach to studying how neural network processes are modulated requires direct monitoring of the TMS-induced changes in brain activity. By combining TMS with other measuring techniques, both the instant and longer-lasting neurophysiological consequences of applying TMS can be assessed (Reithler et al., 2011; Sack & Linden, 2003; Siebner et al., 2009). To be able to monitor what is happening in the rest of the brain while a particular cortical site is targeted can reveal the full network dynamics reflecting the impact of TMS, instead of only assuming certain corollary activation changes or ignoring potential remote effects of TMS altogether (Reithler et al., 2011).

Mottaghy and colleagues (2003) were interested in the temporal dynamics of parietal and prefrontal cortex involvement in verbal working memory (see Buchsbaum, Chapter 32 in this volume). They applied MRI-guided single-pulse TMS to the middle frontal gyrus (MFG) and the IP on each hemisphere. TMS was applied at 10 different time points, 140–500 ms into the delay period of a two-back verbal working-memory task. As a control task, the authors used a choice-reaction task. They discovered different patterns in reactivity when TMS interfered with task accuracy, depending on the brain area that they were stimulating. To be more precise, interference with task accuracy was induced by TMS in the parietal cortex earlier as compared to the prefrontal cortex and earlier over the right than the left hemisphere. They thus showed a clear time-locked main effect in specific brain areas on the accuracy of task performance and concluded that this reveals a propagation of the information flow from parietal to prefrontal cortical sites, advancing faster over the right as compared to the left hemisphere.

Similarly, Schuhmann and colleagues (Schuhmann, Schiller, Goebel, & Sack, 2012) tried to dissect the neural network of language production during picture naming. To do so, they stimulated the left superior temporal gyrus (STG; Wernicke's area), left IFG (Broca's area), and the midsection of the left middle temporal gyrus (MTG) with MRI-navigated, event-related triple-pulse TMS. They stimulated each site, in separate sessions, with pulses applied between 150 ms and 575 ms after picture presentation. Stimulation of all three regions led to a decrease in reaction times; however, the pattern of when the reaction times decreased differed between brain regions. While stimulation of the left MTG led to a decrease in reaction time at 225 ms and again at 400 ms after picture presentation, stimulation of the left IFG had an effect at 300 ms and stimulation of STG at 400 ms, indicating that all areas are functionally relevant for language production, but at different points in time. Thus, by applying TMS over several nodes of the same widely distributed network underlying language processing and production, these studies allow for charting of the relative time points of functional necessity in each of these network nodes, and thereby allow documentation of a certain temporal order of functional relevance between distinct brain regions. This finding clearly shows a specific spatiotemporal organization within the language production network in terms of relative time course in which every area contributes at a different stage during the production process, suggesting distinct underlying functional roles within this complex multicomponential skill (see de Zubicaray & Piai, Chapter 19 in this volume).

Hartwigsen and colleagues (Hartwigsen, Baumgaertner, et al., 2010; Hartwigsen, Price, et al., 2010) took a different approach, and employed a rather novel approach in which they applied rTMS either unilaterally over left- and right-hemispheric regions, or they applied rTMS simultaneously to these regions. By doing so, they wanted to study the inter-hemispheric interaction and compensation mechanisms of phonological decisions. Specifically, Hartwigsen and colleagues (Hartwigsen, Price, et al., 2010) investigated the role of left and right supramarginal gyri during phonological decisions. They applied high-frequency bursts of TMS to either right, left, or bilateral supramarginal gyrus (SMG). The results showed that accuracy and reaction times of phonological decisions were selectively disrupted relative to semantic and perceptual decisions when real TMS was applied over the left, right, and bilateral SMG. This shows that both left and right SMG are needed for accurate and efficient phonological decisions. Moreover, since there was no difference between unilateral and bilateral stimulation, the authors concluded that left and right SMG could not acutely compensate for one another.

To date there are very few studies that have used the advantages of multimodal TMS studies in the field of language research. Fuggetta, Rizzo, Pobric, Lavidor, and Walsh (2009) combined rTMS with event-related potentials (ERPs) to gain insight into the neural basis of the semantic system and in particular to study the temporal and functional organization of object categorization processing. The authors applied short trains of high-frequency TMS over Wernicke's area, the homologous area in the right hemisphere, and a control site while participants were performing a picture-word verification task in which line drawings of natural (e.g., animal) and artifactual (e.g., tool) categories were associated with a word. When Wernicke's area was stimulated immediately before the stimulus onset, the authors observed a delay in reaction times to artifactual items, and thus, an increased dissociation between natural and artifactual domains. This effect was not found after right hemisphere Wernicke's homologous stimulation. Interestingly, the behavioral effect they found had a direct ERP correlate. In the response period, the stimuli from the natural domain elicited a significantly larger late positivity complex than those from the artifactual domain. The authors suggested that this amplitude increase reflects a compensatory transfer of language function from the left to the right hemisphere. These findings demonstrate that rTMS interferes with post-perceptual categorization processing of natural and artifactual stimuli that involves separate subsystems in distinct cortical areas. They also support the view that the representation of semantic knowledge associated with different conceptual domains is based on a network of partially segregated neural systems of functionally interconnected cortical regions. From a cognitive neuroscience perspective, the combination of TMS and ERP is ideal for gaining new insights into the neural basis of a variety of cognitive processes that could not be obtained on the basis of one of these methods alone.

The experimental combination of TMS and fMRI in language research is very rare. Some studies, however, have tried to combine offline TMS with subsequent fMRI. This means that participants first received rTMS outside of the MRI scanner, and were then quickly put into the scanner to see the neural effects outlasting the stimulation duration itself. Hartwigsen and colleagues (2013) did such an offline rTMS study, combining it with immediate fMRI following applied TMS, to research the contribution of the right hemisphere to language production after either the left posterior or anterior IFG was stimulated with an inhibitory TMS protocol. Participants subsequently had to perform an overt repetition task on word and pseudoword stimuli while they were lying in the MR scanner. The authors found that compared to TMS of the anterior IFG, the stimulation of the left posterior IFG decreased activity in the targeted area and increased activity in the contralateral homologous area during a simple pseudoword repetition task (Hartwigsen et al., 2013). They also found an up-regulation of the contralateral homologous area after stimulating the posterior IFG compared to the anterior IFG. Interestingly, when comparing response times, the authors noted that reaction times became faster as the influence of the right posterior IFG on the left posterior IFG increased. This finding shows that homologous areas in the right hemisphere can actively contribute to language production after focal inhibitory stimulation to the left hemisphere. This multimodal TMS study thus revealed the underlying neural effects of TMS and also showed how the brain compensates for a TMS perturbation. These findings also lend further support to the notion that increased activation of homologous right hemisphere areas supports aphasia recovery after left hemisphere damage.

In sum, all of these studies applied innovative and cutting-edge TMS methodology to unravel the dynamic neural network effects underlying language processing. This is particularly valuable, as the complexity of language requires us to look at both the spatial and temporal aspects of distributed neural processing, including task-dependent dynamic changes, direction of information flow, recurrent peaks of functional relevance, as well as remote and compensatory effects following various network perturbations. All of these complex questions can only be addressed using multi-site chronometry TMS and/or TMS in combination with other modalities to directly assess the neural and metabolic consequences of brain stimulation.

TMS as Treatment in Clinical Populations

Aphasia is a common consequence of stroke that typically results from injury to cortical and subcortical structures perfused by the left middle cerebral artery (Hamilton, Chrysikou, & Coslett, 2011; McNeill & Pratt, 2001). While most of the aphasic patients show some degree of spontaneous recovery during the first two to three months post-stroke onset (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Lendrem & Lincoln, 1985; Nicholas, Helm-Estabrooks, Ward-Lonergan, & Morgan, 1993), the majority of patients with post-stroke aphasia are left with some degree of chronic deficit. There is growing evidence that noninvasive brain stimulation can have beneficial effects in the treatment of aphasia (Hamilton et al., 2011).

Several TMS studies have used low-frequency (thus inhibitory) stimulation of the right hemisphere, trying to focally reduce neural activity in the intact hemisphere, contralateral to the lesion (Martin et al., 2004; Naeser et al., 2005). For example, in a study by Martin and colleagues (2004), low-frequency rTMS was applied to four different points on right-hemisphere perisylvian regions in chronic nonfluent aphasics. After stimulation of the right pars triangularis (the right-hemisphere homologue of Broca's area), an improvement in reaction time and accuracy in a picture-naming task was observed. When extending this experiment to a TMS treatment of right pars triangularis stimulation for 20 minutes a day, five days a week for two weeks, significant improvement of picture naming was observed that lasted for up to eight months (Martin et al., 2004). These findings were also replicated by other research teams (Hamilton et al., 2010). Recent studies thus provide the first evidence that TMS might be beneficial in promoting recovery from aphasia after stroke. Future investigations should determine whether combining noninvasive brain stimulation with standard behavioral rehabilitation could lead to even better therapeutic results.

Noninvasive brain stimulation is also starting to play a role in pre-surgical brain mapping. The purpose of pre-surgical brain mapping is to facilitate surgical planning, prevent or reduce morbidity, and optimize the therapeutic effects of surgery (Papanicolaou et al., 2014). Currently, one can identify which hemisphere is the dominant hemisphere for language and memory through the Wada procedure, and which areas underlie somatosensation, motor functions, and language functions with direct cortical stimulation (DCS) mapping. Even though these procedures are the gold standard in pre-surgical brain mapping, research has recently shown that transcranial magnetic stimulation provides equally trustworthy results, and therefore may replace the Wada test and DCS in many, if not most cases. Picht and colleagues (Picht et al., 2013) compared the safety and effectiveness of preoperative TMS with DCS mapping during awake surgery for the identification of language areas in patients with left-sided cerebral lesions. They examined 20 patients with tumors in or close to left-sided language-eloquent regions rTMS before patients received surgery. During awake surgery, language-eloquent cortex was identified by DCS. They observed very good overall correlation between rTMS and DCS, and therefore concluded that noninvasive inhibition mapping with TMS is evolving as a valuable tool for preoperative mapping of language areas.

TMS thus shows promise as a valuable tool in aphasia rehabilitation, and as an alternative to invasive preoperative brain mapping.

OUTLOOK AND FUTURE PERSPECTIVES

In the last 25 years of language research using TMS, our knowledge of the functional role of different brain regions in language processing has increased enormously. As outlined in this chapter, TMS is a very promising tool to help further understand the processes of language processing. As discussed earlier, TMS also has several limitations. However, new methods that are constantly appearing in the field of cognitive neuroscience might help overcome many of these limitations. Among these recently developed techniques, the association of TMS with whole-brain measures of neural functions such as fMRI or EEG (Siebner et al., 2009) has the potential to provide valuable information on the neural network dynamics within language-related brain regions, including deeper cortical areas not directly reachable by TMS. The future of TMS research in language processing therefore lies in employing multimodal approaches to combine non-invasive brain stimulation with neuroimaging techniques. This can be used to validate the assumed neural network changes and to unravel the functional dependencies within these networks, including their relation to various language (sub-)processes. Similarly, computational modeling should be added to the prediction and interpretation of the behavioral consequences of different TMS approaches. This can help to better understand the induced behavioral effects of TMS, to provide concrete models of the underlying mechanism, and to use concurrent TMS and imaging data to further inform, restrict, and validate these models.

Another important future development concerns the application of multi-site TMS protocols, using several smaller focal TMS coils that are still capable of reaching the intended multiple brain regions either simultaneously or with a pre-set inter-coil stimulation delay. This way, several relevant brain regions within the language network can be stimulated at either the same time or in short temporal succession. Consequently, one can directly probe their effective connectivity and directly investigate the complex chronometry of linguistic processes within the millisecond temporal resolution of TMS. Used within clever experimental designs, such multi-site TMS approaches will take advantage of both the neural network dynamics underlying language processing, as well as the excellent temporal resolution of chronometric TMS. Although smaller coils allow more focal and thus spatially isolatable stimulation, in principle, the described problem of spatial overlap within and across language-related brain regions remains. A possible future way of at least partly addressing this issue could come from those experimental TMS approaches that look into the role of state dependency of TMS effects on cognition, using adaptation TMS to specifically target functionally distinct neuronal populations independent of their spatial proximity (Silvanto & Pascual-Leone, 2008).

When it comes to the clinical potential of TMS in the domain of language-related deficits, it seems most promising to conceptualize TMS as an additional treatment to be used in combination with other rehabilitation approaches. TMS can then be used to either prepare the neural network optimally for receiving a given treatment, or to support and guide the adaptive plastic reorganization during rehabilitation. TMS has been shown to enhance and support such recovery processes after brain injury, especially when combined with other therapies to stimulate adaptive reorganization to regain lost functions.

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CHAPTER 6

MAGNETOENCEPHALOGRAPHY AND THE CORTICAL DYNAMICS OF LANGUAGE PROCESSING

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INTRODUCTION

MAGNETOENCEPHALOGRAPHY (MEG) has become an increasingly popular method to study language function in the brain. MEG measures the magnetic field produced by electrical activity generated by cortical neurons. As thousands of neurons become synchronously activated in a cortical patch, the magnetic fields sum up to create a small, but measurable, signal outside the head. The resulting changes in the magnetic field can be tracked with millisecond resolution. Magnetic fields are relatively unaffected by the tissues surrounding the brain (i.e., skull and scalp), thus providing a spatially accurate view of the underlying current sources. Efficient source-modeling techniques enable the reconstruction of cortical sources from the measured signal.

Owing to its combined temporal and spatial sensitivity, MEG can identify different processing stages of cortical processing as they unfold. MEG is thus ideally suited to studying the complex cortical activation sequences that occur during language processing in the brain. Knowledge about timing and location of activation in the brain is important since the same general brain area can participate in multiple stages of language processing, and since the timing of activation can tell us about the specific processing stage at which a particular brain region participates.

MEG provides a versatile set of neural markers for studying language. Evoked responses that are averaged with respect to an external event provide a consistent view of cortical dynamics in language tasks. Cortical rhythmic activity helps to extend and complement the view provided by evoked responses, and connectivity measures can reveal networks that support language processing. Using these neural markers, experiments can be designed to make good use of the strengths of MEG.

Continuous development of source modeling and data analysis techniques allows the study of increasingly complex aspects of language and cognition using MEG. Today, distributed patterns underlying semantic processing (Simanova, van Gerven, Oostenveld, & Hagoort, 2015; Sudre et al., 2012), and global functional networks underlying language (Fonteneau, Bozic, & Marslen-Wilson, 2015; Kujala et al., 2007; Liljeström, Kujala, Stevenson, & Salmelin, 2015) can be studied with a temporal resolution that permits the separation of different processing stages.

In this chapter, we review how neural signaling is picked up by MEG, how source modeling can be used to estimate loci of neural activation, and how MEG has been used to study language (for a more comprehensive description of the MEG method, see, e.g., Baillet, Mosher, & Leahy, 2001; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Hansen, Kringelbach, & Salmelin, 2010). The great advantage of MEG is that it provides the temporal information not available in functional magnetic resonance imaging (fMRI) (see Heim & Specht, Chapter 4 in this volume), and the spatial information not readily available in EEG (see Leckey & Federmeier, Chapter 3 in this volume). However, each measurement technique has its own strengths and limitations. Understanding the limitations and restrictions related to a particular method helps in avoiding common pitfalls and dealing with difficulties and, thus, in producing the best, most reliable brain data. Therefore, we also review problems and common misunderstandings.

How Brain Activity Can Be Detected and Quantified with MEG

Postsynaptic Currents in Populations of Cortical Pyramidal Cells Can Be Detected with SQUIDs

Neural electric currents are extremely weak, and, generally, summation of electric current in tens of thousands of nearby neurons is necessary to render the signal detectable from outside the head. However, not all neural currents are equally well suited for efficient summation. Postsynaptic electric currents in the apical dendrites of cortical pyramidal cells are the main source of the magnetic field recorded with MEG (and the electric potential recorded with electroencephalography, EEG). The parallel orientation of the neighboring apical dendrites and the relatively long duration of the postsynaptic potential (~10 ms) can raise the local population-level electric current to a detectable level. Further, the postsynaptic electric current is dipolar in nature, and the resulting dipolar magnetic field persists furthest in distance. In contrast, for example, an action potential lasts only about 1 millisecond (ms), and its quadrupolar field dies away rapidly with distance.

Even the strongest magnetic fields generated by regular cortical activity are extremely weak in absolute terms, on the order of 100 femtotesla (but can be markedly stronger for epileptic spikes). While noninvasive recording of the brain's magnetic fields was first demonstrated with coils of copper wire (Cohen, 1968), much more sensitive devices were needed for MEG to have any practical use. The necessary sensitivity came in the form of superconducting quantum interference devices (SQUIDs). By exploiting weak links in a superconducting ring (Josephson junction), SQUIDs serve as highly sensitive transformers of magnetic field into measurable voltage. Optimal sensitivity is achieved by making SQUIDs rather small. As a result, they couple only weakly to magnetic fields. Thus, viable MEG recordings require the use of superconducting flux transformers, composed of a pickup coil and a signal coil that bring the magnetic field to the SQUIDs.

The Pickup Coil Geometry Influences the Sensor-Level Appearance

The geometry of the pickup coils determines the component of the magnetic field that is measured and the appearance of the recorded sensor-level MEG signals. Pickup coils are typically formed of just one wire loop (magnetometer, measuring the absolute field component) or by two oppositely wound loops (gradiometer, measuring the spatial gradient of the field). Magnetometers have the best depth sensitivity but, for the same reason, they also readily pick up signals from sources other than the brain (noise from the brain-signal recording point of view). Gradiometers cancel out magnetic fields from faraway sources and are most sensitive to nearby cortical sources. In an axial gradiometer, two oppositely wound loops are placed one above the other, and the distance between the loops determines the depth sensitivity; with an increasing distance between the two loops, an axial gradiometer approaches a magnetometer. In a planar gradiometer, the oppositely wound loops are placed on a plane, side by side, forming a figure eight (cf. Figure 6.1).

The sensor-level appearance of the different types of pickup coils is remarkably distinct. Magnetometers and axial gradiometers detect the maximum value over the field maximum, whereas planar gradiometers detect the maximum value over areas where the magnetic field shows the most rapid spatial change. Thus, as illustrated in Figure 6.1 for a dipolar magnetic field, magnetometers and axial gradiometers detect two maxima, a positive and a negative one on both sides of the source of electric current (neural activation), and no signal directly above the source where the field strength is zero. The planar gradiometers, instead, detect one maximum directly above the source, where the magnetic field derivative is strongest, and the signal dies away with distance from

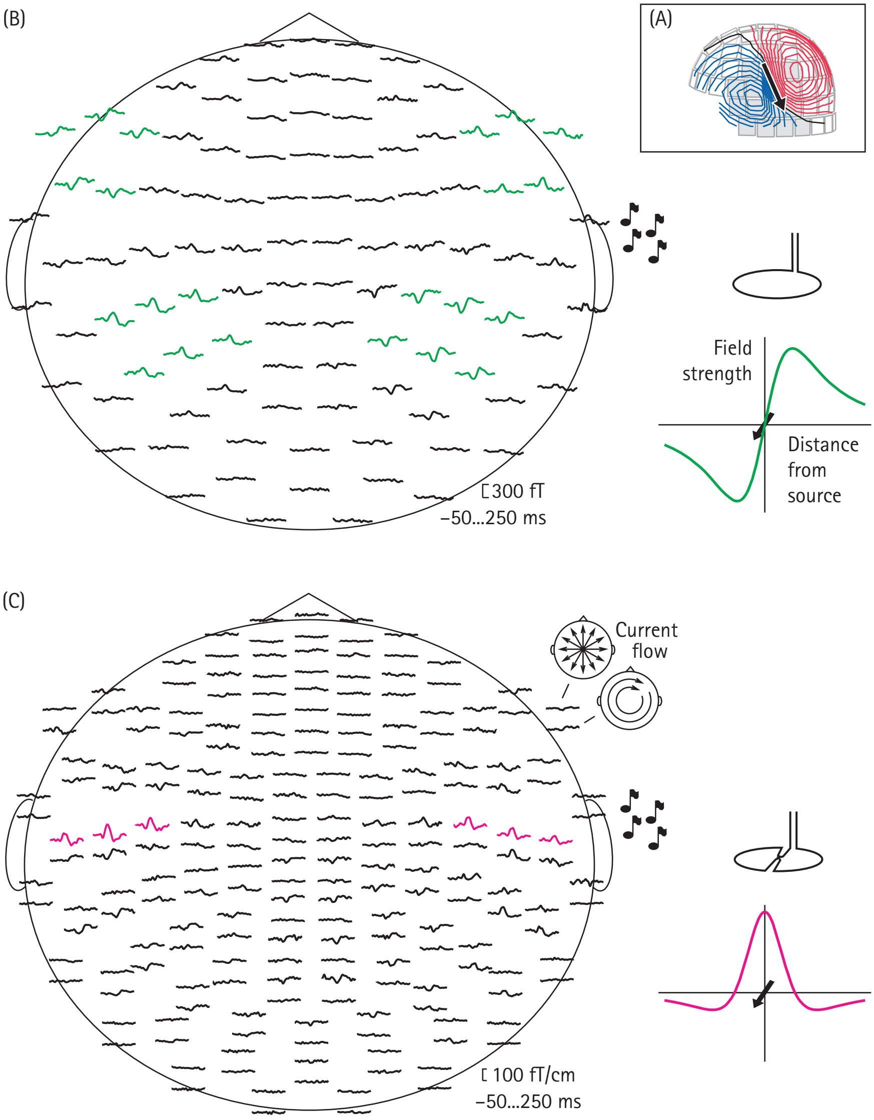


FIGURE 6.1. Influence of pickup coil geometry on the MEG sensor signals. (A) Magnetic field pattern recorded over the left hemisphere at ~100 ms after auditory stimulus onset. The black arrow indicates current flow in the auditory cortex (direction perpendicular to the course of the Sylvian fissure). The red area indicates magnetic field emerging from the brain, and the blue area indicates the re-entering field. These data were recorded with the Elekta Neuromag device, which has both planar gradiometers (two orthogonal sensors) and magnetometers at the same 102 locations. (B) Magnetometers, or axial gradiometers, detect two maxima, one negative and the other positive, on both sides of the current. The signal is zero directly above the source. The measurement helmet is flattened onto a plane and viewed from above, with the nose pointing upward. Each curve denotes the change of magnetic field as a function of time, from 50 ms before to 250 ms after stimulus onset. (C) The planar gradiometers detect one maximum, directly above the source current, where the field gradient is largest. Thus, the sensor array now displays only a single area of strong deflections in each hemisphere, above the auditory cortex.

the source. When there are only a couple of salient, spatially distinct sources, such as in passive listening to short tones, it is easy to discern the rough source configuration directly at the sensor level, regardless of the type of pickup coil.

MEG Signals Pass Through the Skull and the Scalp Unaffected

The closely spherical geometry of the head, with conductivity changes occurring primarily along the radius (brain–skull–scalp), has important consequences for electromagnetic fields. Theoretically, it can be shown that in the special case of a sphere where the conductivity changes occur only along the radius, a dipolar current source generates a (component of) magnetic field that reflects the intracellular current flow (commonly referred to as primary current), with no influence of the volume/return currents (Hämäläinen et al., 1993). Although the human brain is obviously not fully spherical, nor does it have homogeneous conductivity, the conductivity changes tend to be locally quite radial, and the contribution of volume currents is markedly lower than in EEG. Thus, the spatial profiles of EEG and MEG differ considerably. The passage from the highly conducting brain tissue through the poorly conducting skull to the highly conducting scalp strongly affects the volume currents, resulting in considerable spatial blurring of EEG recordings (where the cortical electric field is sampled at the scalp). The MEG signals recorded from outside the head are, however, essentially the same that would be recorded on top of the cortex, with the skull removed (for empirical evidence, see Okada, Wu, & Kyuhou, 1997).

The approximate spherical symmetry has further consequences for the recorded MEG signals. Dipolar currents that are oriented fully along the radius do not generate a measurable magnetic field. The pyramidal cells are oriented normal to the cortical surface, which means that activation strictly limited to the gyral crown or sulcal base might remain undetected with MEG. All the other signals that are even slightly tilted from the radial orientation are readily observed. The tangential current flow in the sulcal walls is optimally detectable with MEG. Notably, in cognitive processing, activation is also unlikely to be limited to the very narrow cortical areas of fully radial current flow.

Real-Time MEG Signals Facilitate Several Complementary Views into Brain Function

In a sense, electromagnetic recordings are like a blood sample: when the data are collected with a fairly liberal bandwidth (e.g., 0.01–200 Hz) and stored in their full form, one can later extract many types of measures from them. An evoked response is the (presumably) invariable neural activation that always occurs at the same time with respect to a certain event. Since the brain is constantly involved in many operations, the electrophysiological brain signals show plenty of modulation that is unrelated to the task of interest. This unwanted "noise" is diminished by averaging responses across multiple trials of the same type (e.g., presentation of real words or pseudowords). Averaging the wide-band signal with respect to a certain trigger point, such as a stimulus or movement onset or offset, should highlight the evoked responses tightly linked to those events. The evoked response is strongest to stimulus changes, and the signal typically starts to diminish after ~1 second (s) from the trigger. The highly reproducible and informative evoked response continues to be the most commonly used descriptor of neural engagement.

By performing a different type of analysis, the background "noise" may reveal other valuable information about brain processes. Using spectral analysis, one can show that the cortical cell populations display spontaneous oscillatory activity, most saliently at around 10 Hz (often referred to as "alpha") and 20 Hz ("beta"). This activity is strongest when the individual is resting, with eyes closed (Hari & Salmelin, 1997). Event-related time-frequency (TFR) analysis has further demonstrated that induced oscillations (i.e., stimulus- and task-related modulations) may appear at a much wider range of frequencies, from around 5 Hz ("theta") to 90 Hz ("low gamma" 30–60 Hz, "high gamma" 60–90 Hz). Frequencies up to about 30 Hz reflect actual oscillatory processes with fairly well-defined spectral peaks, whereas the gamma range activity may denote also more arrhythmic processes, possibly related to spiking activity (He, Zempel, Snyder, & Raichle, 2010). While there are many suggestions of the possible functional roles of the different frequency ranges (Bastos et al., 2015; Donner & Siegel, 2011), a unified interpretation is still lacking. In TFR analysis, the signal power per frequency bin is averaged across multiple trials, with information of signal phase omitted; thus, the resulting event-related (or induced) modulations reflect time-locked but not necessarily phase-locked activity. Accordingly, the event-related modulations of band-limited power are less sensitive than evoked responses to inter-trial jitter in task timing. Generally, the modulations of rhythmic activity tend to be quite slow, peaking and lasting from hundreds of milliseconds to seconds after the event. The evoked responses and event-related power modulations in various frequency bands provide markedly distinct windows into brain processes (Laaksonen, Kujala, Hultén, Liljeström, & Salmelin, 2012) (Figure 6.2).

Source Models Allow Estimation of the Loci of Neural Activation

MEG sensors record electromagnetic fields of all ongoing neural activity at once. This is different from, for example, fMRI where the full image is generated by probing one area at a time. Even though the coupling between a neural source and an MEG sensor varies over space, each source is seen by all sensors (field spread) and thus the signal at each sensor is a weighted sum of signals from all sources. Estimation of the spatial loci of the neural currents from electromagnetic field patterns requires modeling of the source currents and the conductivity profile of the human head (spherical or realistic head model). However, there is no single optimal way to model the source structure

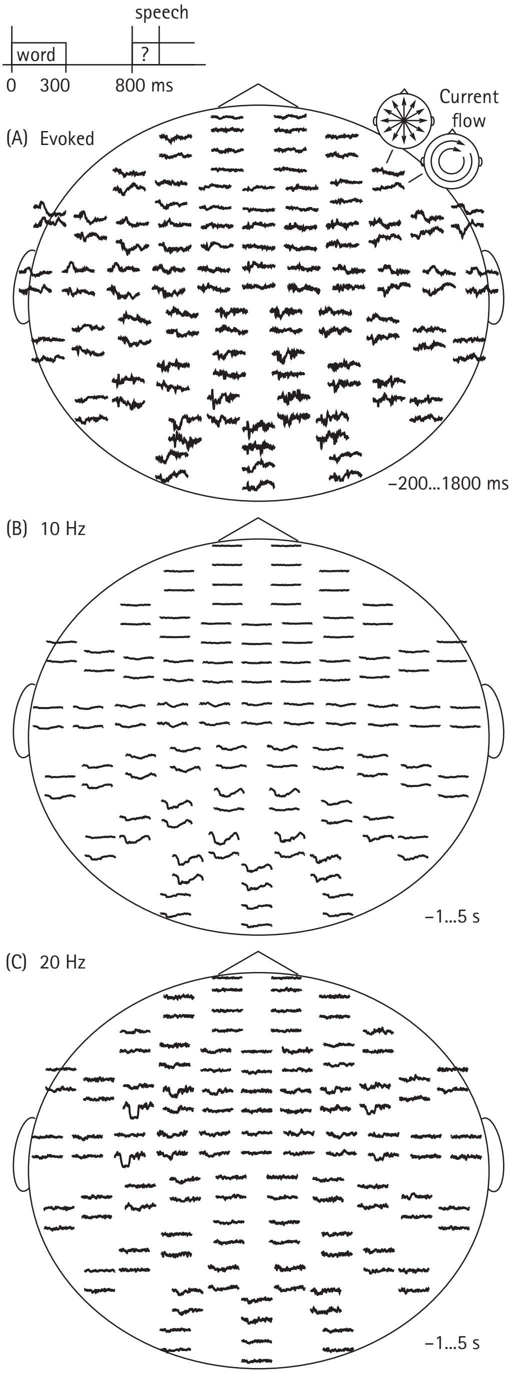


FIGURE 6.2. Evoked responses and cortical rhythms provide different views into brain function. In this experiment, a word was presented at time 0, for 300 ms. After an interval of 500 ms, a question mark appeared at 800 ms, prompting the subject to read the word out loud. Each trial lasted for about 5 seconds. (A) Evoked responses extending over a period of 2 s, including a 200 ms pre-stimulus baseline interval. There is plenty of activation all over the cortex, especially within about 1 s after stimulus onset. (B) Event-related modulation of the mean amplitude of 10-Hz oscillations from the same data. The time window extends from 1 s before word onset to 5 s after it. Modulation, primarily suppression, occurs over occipital and posterior parietal areas. (C) Event-related modulation of the mean amplitude of 20-Hz oscillations from the same data. The time window extends from 1 s before word onset to 5 s after it. The effect is, again, mainly suppression, but now occurs along the central sulcus.

for reaching from the measured distribution of magnetic field at the sensors to cortical distribution of neural current flow. While the forward problem from neural sources to magnetic field is neurophysiologically, physically, and mathematically well described and understood (Hämäläinen et al., 1993; Lopes da Silva, 2010; Okada et al., 1997), the inverse problem (i.e., going in the opposite direction to determine the active brain areas and the time courses of activation from the measured magnetic fields) is more challenging. A single current dipole is a reasonable equivalent descriptor of focal cortical current flow at the typical measurement distance from the cortex (>3 cm). The commonly used MEG source estimation approaches, all employing a current dipole as the source model, can be divided into discrete current-dipole models, distributed source estimates, and beamformers.

The equivalent current dipole (ECD) approach assumes that the measurements are generated by one or more active sites in the brain, with each site small enough to exhibit a salient dominant direction of neural current flow that can be well described with a current dipole as an equivalent source. One identifies the ECD locations, orientations, and amplitudes that best match the measured MEG data in the least-squares sense. Typically, a relatively small number (up to 10) of spatially and/or temporally separable ECD components suffice to account for the MEG data, even in higher cognitive tasks such as language processing (Salmelin, 2010). The distributed source estimates consider a continuous spatial distribution of current dipoles, often restricted to a cortical grid determined from the participant's individual MRI data. The commonly employed minimum norm estimate (MNE; Gramfort et al., 2014) assumes that the distribution of current with the minimum overall power among those capable of explaining the data is the best source-level solution. Although there is no neurophysiological information to argue for minimization of overall power or amplitude as a relevant criterion, the approach is mathematically appealing. Both ECD and MNE have proven to be efficient tools for characterizing cortical dynamics of sensory and motor as well as language and other higher cognitive processing, as evidenced by evoked responses.

Beamforming is a somewhat different approach, in which the brain volume is scanned by sequential application of a spatial filter that is optimized to pass activity from a specific brain area at unit gain while suppressing activity from other areas. To achieve such suppression, one has to assume that none of the other sources is temporally correlated with the target location (Van Veen & Buckley, 1988); while brain regions commonly do display correlated activity, the correlations between them are normally lower than would be needed to markedly affect the beamforming suppression (Gross et al., 2001). A current dipole again serves as the elementary model of neural activity at each tested grid point. The implementation of beamformers entails the use of a data covariance estimate to construct the spatial filter. Beamformers have been successfully applied to the power mapping of MEG data in the time (Robinson & Vrba, 1997) and frequency domains (Gross et al., 2001; Laaksonen, Kujala, & Salmelin, 2008; Liljeström, Kujala, Jensen, & Salmelin, 2005) and to the estimation of cortico-cortical coherence (Gross et al., 2002; Kujala et al., 2007) in various tasks.

While source modeling of electromagnetic fields may require some thought, the relatively straightforward access to the time courses of source-level estimates of activation is the great strength of MEG. The magnetic field is not markedly blurred by conductivity changes in different parts of the head, and the specific sensitivity to the tangential component of the neural currents greatly simplifies the calculations and interpretations. Indeed, brain-level description of activation, from individual participants to the group level, has always been at the core of the MEG method. Most important, MEG facilitates the use of reasonably accurate spatial information as a powerful means of decomposing the sensor-level time courses to separable, functionally meaningful neural-level time courses.

MEG Facilitates Analysis of Real-Time Connectivity

MEG is well suited for exploring task-related brain networks as it facilitates direct estimation of neurophysiological connectivity measures that can be linked to specific cortical areas. There are two main approaches for studying cortical interactions with MEG. First, one may describe connectivity within an experimental condition using connectivity measures that minimize sensitivity to field spread (Nolte et al., 2004; Stam, Nolte, & Daffertshofer, 2007). Second, it is possible to evaluate connectivity differences between experimental conditions when their power levels, and thus field-spread properties, are comparable (Kujala, Vartiainen, Laaksonen, & Salmelin, 2012; Schoffelen & Gross, 2009).

The rich temporo-spectral content of the MEG signal allows the use of various metrics and approaches for characterizing interactions between brain regions. As regards frequency-specific interactions, coherence among brain regions is thought to constitute a mechanism through which information is transferred within cortical networks (e.g., Fries, 2005). Using coherence as the measure enables direct whole-cortex mapping of connectivity at different frequencies without the need to estimate time series at the level of cortical sources (Kujala, Gross, & Salmelin, 2008). Coherence reflects both amplitude and phase co-modulation between areas. One may reduce the effects of amplitude fluctuations by focusing on the phase dynamics of the signals (Palva & Palva, 2012; Simões, Jensen, Parkkonen, & Hari, 2003). Moreover, the temporal specificity of MEG signals facilitates the evaluation of directed interactions between regions, for example, using Granger causality (Barnett & Seth, 2014; Geweke, 1982; Kujala et al., 2012; Michalareas, Schoffelen, Paterson, & Gross, 2013) or dynamic causal modeling (Daunizeau, Kiebel, & Friston, 2009; Woodhead et al., 2014), typically among predefined seed regions (activation or coherence maxima).

Although the field-spread effects combined with the rich spectro-temporal content of the MEG signals make reliable evaluation of neural connectivity with MEG technically challenging, the recent years have seen important technical and conceptual advances (Kujala et al., 2008; Nolte et al., 2004; Palva & Palva, 2012; Schoffelen & Gross, 2010) that have enabled the successful quantification of cortico-cortical interactions in the resting state and in various task modalities, with both MNE and beamforming (Gross et al., 2002; Jerbi et al., 2007; Kujala et al., 2007; Palva, Monto, Kulashekhar, & Palva, 2010). Connectivity analysis facilitates the study of continuous, increasingly naturalistic tasks (Kujala et al., 2007), but can equally well be applied to event-related paradigms (Palva et al., 2010), as long as there are enough data to reach reliable estimates. Interconnected functional networks may be formed by multiple brain areas (Gross et al., 2002) or by loops formed by muscles (electromyography, EMG) and the brain (Butz et al., 2006).

Methodological Considerations

Artifactual Signals Should Be Identified and Excluded as They Can Confuse the MEG Patterns or Be Misconstrued as Neural Activation

Any remaining magnetic material in the body (e.g., from accidents or surgery) or on the body (e.g., watch, jewelry, underwire bra, permanent hair or eyelash coloring) may move with breathing or body movements, generating an electromagnetic field. These signals are far stronger than brain signals, but their sources can usually be identified and often removed (Hansen et al., 2010). The heartbeat generates a strong field, which can be notably picked up by the MEG sensors, especially in children. Because of the very distinct spatiotemporal pattern of heartbeat that differentiates it from brain signals, the heartbeat artifact can usually be efficiently removed using principal or independent component analysis (PCA, ICA; Gross, Baillet, et al., 2013) or temporal signal space separation (tSSS; Taulu & Simola, 2006) methods.

Electromagnetic signals from eye blinks and movements, as well as face, tongue, and neck muscle activity also far exceed the strength of brain signals. Methods like PCA, ICA, and tSSS can help to reduce those artifacts, but as their spatiotemporal patterns are relatively similar to those of brain signals, it is practically impossible to completely remove these types of artifacts without risking concomitant removal of relevant brain activity. Accordingly, whenever possible, it is best to make every effort to minimize those sources of artifacts in the experiments, or to focus on time windows where they are minimally present (as evaluated by electro-oculogram, eye tracking, electromyogram, etc.). Averaging across multiple trials can further reduce the (remaining) effect of artifacts unless the task is such that, for example, participants tend to make inadvertent, small eye movements more consistently and time-locked to one stimulus category than another.

A remaining eye movement artifact can be problematic for functional interpretations. Figure 6.3 illustrates the source level appearance of an eye blink. The field has a characteristic pattern with negative values in one hemisphere and positive values in the other, with strong maxima in the front. The ECD solution does not have to be restricted to a

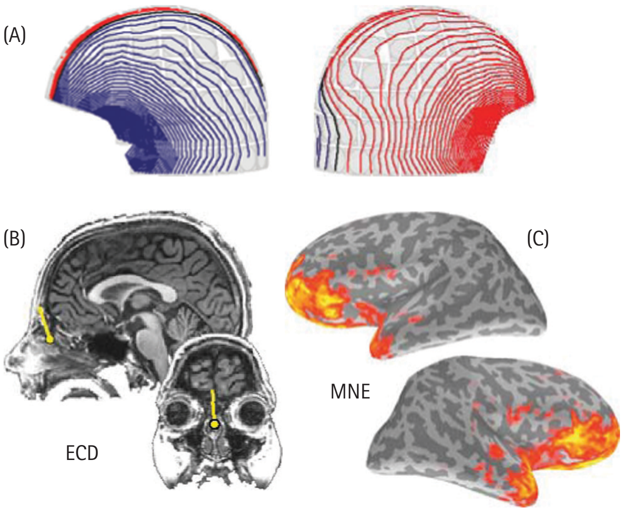


FIGURE 6.3. Eye blink artifact appearing at the source level. (A) Field pattern of MEG signals associated with eye blinks. (B) ECD analysis finds the source between the eyes, well outside the brain. (C) Anatomically constrained MNE analysis restricts the solution to the cortex. The blink artifact is mapped to the cortex as well. The signal seems to be generated, incorrectly, in the left inferior frontal and anterior temporal cortex.

specific volume, and it can usually pinpoint artifactual sources as they tend to localize outside the brain. Here, the ECD analysis localizes the source between the eyeballs. Distributed methods, in order to attain reasonable spatial specificity, confine all source estimates to the cortical surface. Thus, regardless of whether the signals are actually generated in the cortex or elsewhere, they are mapped to the cortex. Here, the MNE estimate of cortical activation clusters in the inferior prefrontal and anterior temporal lobes (Figure 6.3 C). It is worth noting that the most anterior and inferior parts of the frontal and temporal cortices are also the areas that are usually least optimally covered by the MEG helmet and, therefore, typically have the lowest signal-to-noise-ratio (SNR). These general areas are often associated with high-level cognitive processes, including language processing (Vigneau et al., 2006). Careful removal of eye movement artifacts is thus of utmost importance in MEG studies of language.

In studies of language production, artifact signals from the face, mouth, and tongue muscles are unavoidable. Depending on the research question, one may try to minimize their effect on the brain signal analysis by focusing on the interval when the overt response is being prepared but not yet executed, or by using an experimental design where the overt response is delayed. An alternative approach is to try to isolate the magnetic field pattern related to the mouth movement artifact as cleanly as possible. This may be successful in situations where salient trigger points can be identified separately for stimulus presentation, mouth movement (from electromyography recording), and speech onset (from microphone recording). When the relative onsets of these three stages jitter across trials by a few hundred milliseconds, it is possible to highlight the speech production artifact by averaging the MEG signals with respect to the microphone onset without picking up too much of the cortical activation time-locked to stimulus or speech onset, as those signals mostly average out (Salmelin, Schnitzler, Schmitz, & Freund. 2000; Salmelin, 2010). The artifact related to speech production typically shows signals that are strongest at the rim of the sensor array, centering above the cheek area (Figure 6.4 A). When this field pattern is removed from the evoked response time-locked to mouth movement onset, salient focal activation is revealed over the frontal lobes that localizes to the face representation area in the sensorimotor cortex bilaterally (Figure 6.4 B) (Salmelin, 2010). Even when there are no triggers to guide the artifact extraction, it may be possible to sufficiently suppress the artifact (e.g., using PCA or ICA). However, the success of this exercise should be carefully evaluated, as it depends heavily on the experimental design and the type and amount of artifacts in the experimental conditions to be contrasted.

When the actual experimental response is, or could be, mixed with non-brain artifact signals, caution is warranted in analysis and interpretation. It is possible that the observed source-level patterns are partly artifact driven, especially in brain areas where the sensitivity of the MEG method (or measurement helmet) is not very high. In such regions (e.g., basal temporal cortex and anterior and medial frontal cortex), any remnants of major external artifacts or small but systematic movements (muscle activity) of the eyes, face, neck, tongue, and so on, that tend to occur more regularly with one stimulus category than another can falsely be interpreted as neural activation, especially when using cortically constrained distributed source models.

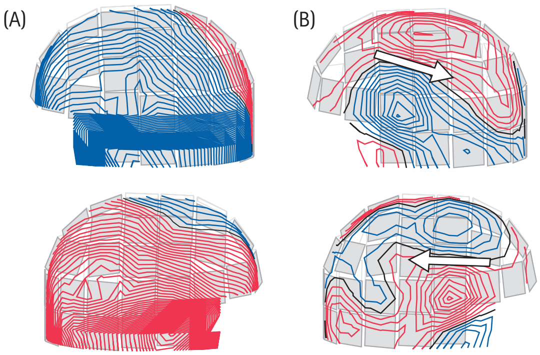


FIGURE 6.4. Artifact signal associated with speech production. (A) Field pattern of MEG signals reflecting artifactual muscle signals during spoken word production (time 0 with respect to microphone signal onset). (B) Field pattern of MEG signals time-locked to mouth movement in spoken word production (20 ms after the onset of the electromyogram signal recorded from mouth muscles), where the artifact field in (A) has been projected out. The white arrow represents the ECD that best accounts for the local magnetic field pattern. The left side of the MEG sensor array is shown above, the right side below.

Source: Modified from Salmelin (2010).

Focal and Distributed Source Models Each Have Their Strengths and Limitations but Neither of Them Yields the Actual Spatial Extent of the Active Areas

Focal and distributed source models each have their strengths and limitations. Efficient high-quality multi-ECD modeling requires experienced user intervention. However, it also simultaneously encourages a thorough familiarization with the data, which importantly helps to avoid misinterpretations. MNE provides a fairly automatic approach to source-level mapping, but when the solution is forced to the cortical surface any possible artifact signals are also mapped to the cortex. It is not possible to define an absolute threshold of meaningful activation strength in distributed maps; in the focal model, this translates to the difficulty of deciding how weak a source should still be included in the model. The most salient source-level activity never goes undetected in either distributed or focal analysis. MNE provides an estimate of current strength at all cortical locations, whereas ECD gives non-zero values only at the hot spots of activation, but then also provides an estimate of the dominant direction of current flow in that locus. The ECD and MNE methods are thus partly complementary. The choice of the primary approach is best determined by the research question. Ideally, one would use both focal and distributed modeling to reach a valid source-level description and interpretation.

Source modeling yields estimated sites of local maxima of activation, but neither focal nor distributed estimates reflect the true extent or shape of the cortical activation. Regardless of whether the actual source in the brain is spatially highly focal (as is probably the case for early sensory activations) or more extended (as might occur for high-level cognitive processes), it will appear focal in ECD and distributed in MNE: this is a direct manifestation of the ill-posed nature of the electromagnetic inverse problem. Independent of the true extent of the sources, both focal and extended source-level models can be equally good in explaining the measured magnetic fields. While it seems that many experimenters may be able to accept that the distributed MNE map could actually reflect more focal neural activity, it may be less obvious that, owing to the considerable distance of the sensors from the sources, an ECD may equally well serve as an excellent equivalent representation of an extended source ("regional source") (Scherg, 1990).

Smoothness of the Electromagnetic Field Is Both an Asset and a Nuisance

The electromagnetic field is inherently smooth: small dislocations of the source currents can have a fairly small effect on the spatial configuration of the field. The magnetic field generated by a current dipole (see Figure 6.1) is modulated more markedly when the source location changes in the direction perpendicular to the source current, rather than along the current flow. Similarly, the field pattern is not very sensitive to changes of source depth. However, any change of the orientation of the current flow, while the location remains unchanged, has a strong effect on the field pattern. Although the inherent smoothness of the magnetic field often hampers accurate localization of neural currents, it simultaneously has the benefit that small differences in source localization have very little influence on the estimated time courses of activity in that general source area. Thus, the MEG-derived regional time courses can be highly accurate even when there may be some uncertainty in the source locations. Indeed, an important beneficial consequence of the inherent spatial smoothness is that the exact choice of the areal extent and shape of activation in a distributed model is not critical for an accurate estimation of activation time courses, as long as the selection includes the local maximum. Nor does some variation in the focal ECD parameters compromise the accuracy of the time course of the neural activation it describes. MEG-based "regions of interest" may thus be most appropriately referred to as "regional labels."

Because of the inverse problem and the smoothness of the field pattern, MEG cannot boast high absolute accuracy of source localization, except in the rare cases of early sensory responses when essentially only one cortical locus shows activation. When that happens, for example, for somatosensory stimulation of the hand, the hand representation area in the primary somatosensory cortex can be localized with an accuracy of a few millimeters. This type of mapping has great clinical value in preparation for surgical treatment of tumors, stroke, and epilepsy. Systematic relative differences between sources can often be determined with very good accuracy (e.g., representations of different digits in the hand area; Forss, Jousmäki, & Hari, 1995). In language tasks, multiple brain areas are active simultaneously, and the "noise" from other active sources can hamper the localization accuracy of individual sources; in practice, the localization accuracy is in the centimeter rather than millimeter range. As regards spatial resolution, two dipolar current sources located next to each other, with the same direction of current flow, can usually be differentiated if they are at least 2 centimeters apart (Liljeström, Kujala, Jensen, & Salmelin, 2005). However, the more dissimilar the directions of current flow, the better dissociable are the sources. Moreover, distinct time courses of activation can help immensely in differentiating between spatially close sources.

Connectivity Estimates Can Be Severely Confounded by Field Spread

Because all MEG sensors see the signals from all neural sources, to varying degrees, sensor-level estimates of connectivity are deeply confounded (Schoffelen & Gross, 2009). Indeed, source-level estimates are particularly critical in connectivity analysis. However, the estimated cortical time courses are not entirely free from the problematic effects of field spread, either. While it is formally possible to compute connectivity measures between time series estimated for any brain areas, caution is necessary.

If the field-spread effects are not properly taken into account, one may obtain spurious estimates of connectivity. It would be particularly easy to misinterpret changes in the level of activity between conditions as changes in the level of interaction across brain regions; such effects are especially prominent when considering nearby sources. Moreover, as connectivity measures are generally very sensitive and can pick up comodulation in low-amplitude signals, they also readily detect spurious effects from small remnants of external artifacts. Thus, in MEG connectivity studies, it is even more imperative than in activation studies to collect high-quality data and to ensure that the detected effects do indeed have a cortical origin.

Different measures of connectivity are optimally suited for different types of analyses. For example, resting-state connectivity is frequently assessed using the imaginary component of coherence as the measure, which helps to reduce the effect of field spread (Marzetti et al., 2013). As imaginary coherence is sensitive only to time-lagged synchronization, the instantaneous field spread from a single neural generator does not lead to spurious connectivity between separate brain areas (Nolte et al., 2004). However, as information about the absolute amount of coherence is simultaneously lost, imaginary coherence is best suited for the study of isolated experimental conditions, such as the resting state, where the interest is primarily in whether there might be a link with another area. This measure is less optimal for estimating functionally relevant changes of connectivity between experimental conditions, which is typically the focus of cognitive studies. In those cases, it is better to consider the full coherence and to reduce the effect of field spread by limiting the functional interpretation to long-distance connections. When contrasting connectivity between two conditions, it is essential to ensure that their power levels do not differ markedly in the time and frequency ranges of interest (Kujala et al., 2012; Schoffelen & Gross, 2009, 2010).

Spatial Dependence of Distributed Source-Level Estimates Must Be Taken into Account in Statistical Testing

While it is formally possible to calculate fMRI-type whole-head contrasts between distributed source-level MEG estimates, such estimates do not reflect source size or shape, and the interpretation of any resulting differences can thus be problematic. The values at the neighboring voxels or grid points are spatially highly dependent, and the maps should be considered in their entirety, taking properly into account the effects of the point-spread functions of the source estimates and crosstalk between cortical regions; cluster-based statistics (Maris & Oostenveld, 2007) may be developing toward this goal.

A regional label approach helps to circumvent the issue of field spread, to a reasonable degree, as functional differences are then compared between conditions per source areas whose shape and size are kept constant. One reasonable approach is an omnibus search in which regional labels are selected from activation maps pooled across all experimental conditions and participants, and the signal values within those regions are then evaluated per condition, per participant (Hultén, Karvonen, Laine, & Salmelin, 2014; Lee, Hämäläinen, Dyckman, Barton, & Manoach, 2011). In ECD modeling, the corresponding omnibus approach identifies ECDs that account for the data across conditions, per participant, and then cluster them across participants into groups by similarity of location, direction of current flow, and time course of activation (Hultén et al., 2014; Salmelin, 2010). It is also possible to use a priori brain atlas divisions, as long as the entire cortex is considered at once. However, the local activation maxima may not fall neatly onto a single atlas division, as existing brain atlases are mostly based on anatomical segregation. Furthermore, using sulci as dividing lines is problematic for MEG, which is most sensitive to activity within the sulci but cannot readily tell apart the two opposing sides of a sulcus.

HOW LANGUAGE FUNCTION MAY BE STUDIED WITH MEG

Evoked Responses Provide a Consistent View of Cortical Dynamics in Language Tasks

Evoked responses are the trustworthy workhorse of electromagnetic brain mapping. Two decades of research using evoked MEG responses have resulted in a solid view of cortical dynamics in written and spoken word processing, as well as in picture naming (Salmelin, 2007), that has been further exploited to address more specific questions: for example, the neural correlates of semantic representation and composition (Halgren et al., 2002; Helenius, Salmelin, Service, & Connolly, 1998; Pylkkänen, Bemis, & Blanco Elorrieta, 2014; Pylkkänen & Marantz, 2003; Vartiainen, Parviainen, & Salmelin, 2009); morphosyntax (Friederici, Wang, Herrmann, Maess, & Oertel, 2000; Pylkkänen, Feintuch, Hopkins, & Marantz, 2004; Service, Helenius, Maury, & Salmelin, 2007; Vartiainen, Aggujaro, et al., 2009); language learning (Dobel et al., 2010; Hultén et al., 2014; Nora et al., 2012); and developmental language disorders (Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Parviainen, Helenius, & Salmelin, 2005; Salmelin, Schnitzler, et al., 2000).

MEG is well suited for the study of speech perception. Auditory signals, including speech, evoke a typical sequence of responses in the Heschl's gyrus and the adjacent temporal sulci that is readily picked up by MEG. The auditory cortex is first activated at ~15 ms (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994) after an auditory stimulus, but salient detection of the earliest responses (<50 ms) usually requires hundreds of repetitions of the same stimulus, which is typically not an ideal paradigm for language studies. However, a strong transient response at ~100 ms after stimulus onset ("N100m") may in some cases stand out from the background activity, even in a single trial. Although the time window of the N100m response has been associated with acoustic-phonetic processing, a fairly low-level process in speech perception (Parviainen et al., 2005; Tiitinen, Mäkelä, Mäkinen, May, & Alku, 2005), in neurophysiological terms N100m is a rather late cortical response. Studies using an oddball design (i.e., repeated presentation of a certain stimulus, randomly interrupted by a different, rare stimulus) have indicated that phonemes are distinguished by ~150 ms (Näätänen et al., 1997; Vihla, Lounasmaa, & Salmelin, 2000).

The time course of lexical-semantic processing in spoken word perception has been probed with various types of stimulus and task manipulations and has been associated most consistently with the onset phase (~200–400 ms) of a strong sustained activation that typically lasts from about 200 to 800 ms after word onset (Helenius et al., 2002). The phenomenon of sustained auditory cortical responses, as such, is not limited to linguistic stimuli. Sustained responses are evoked by environmental sounds (Renvall, Formisano, et al., 2012) and even by long-duration meaningless auditory stimuli (Eulitz, Diesch, Pantev, Hampson, & Elbert, 1995). Furthermore, it is important to realize that none of the responses and time windows of activation can be associated solely with one function; rather, some degree of modulation of the evoked response strength or timing typically can be linked with a specific processing stage.

From the MEG point of view, when advancing in time, the cortical locus of the evoked response to spoken words in and around the auditory cortex remains essentially the same (Figure 6.5). However, it may be possible to demonstrate, at the group level, that the center of activation shifts between different time windows or experimental conditions (e.g., between ipsi- and contralateral responses to tones (Parviainen et al., 2005)). Furthermore, within the source region it is possible to identify substructures that display unique time courses of activation. Figure 6.5 illustrates group-level distributed MNE and focal ECD estimates when participants were listening to spoken words, knowing that they would be expected to subsequently reproduce each word (Nora et al., 2012). The MNE view illustrates how activation remains in the same superior temporal locus (Figure 6.5 A). The ECD analysis can further exploit MEG's sensitivity to the orientation of neural current flow. Across individuals, ECD analysis identifies two consistent clusters within this same general region, one with superior-inferior current flow, indicating neural activation in the lower lip of the Sylvian fissure, and the other with a posterior-anterior current flow. The two types of sources have very different time courses of activation (Figure 6.5 B) and different reactivity to experimental manipulation, and thus different functions (Nora et al., 2012; Nora, Renvall, Kim, Service, & Salmelin, 2015). Here, MNE and ECD analyses, together, confirmed the spatiotemporal pattern of cortical activation, and the substructure obtained with the ECD analysis allowed to extract remarkably clean time courses of activation for detailed functional analysis.

The accurate temporal information linked with brain areas provides a unique view to brain function. For example, the MNE sequence in Figure 6.5 also suggests a weak activation in the frontal cortex, which was identified with ECD analysis as well (not shown). Motor or premotor cortical activation during the phase of spoken-word perception may

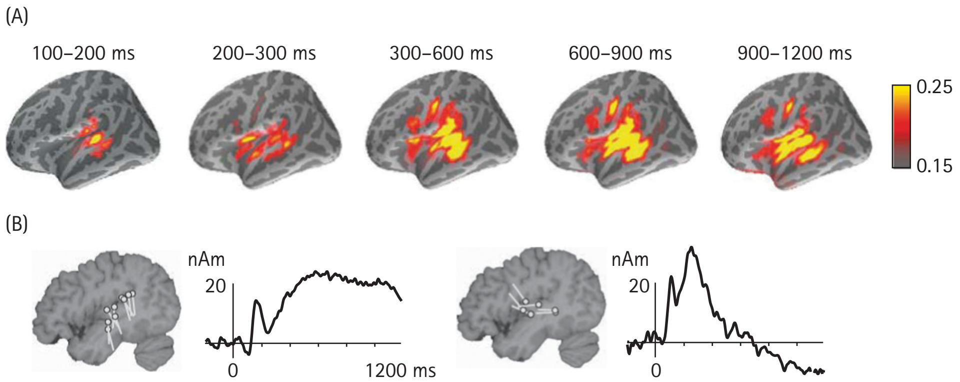


FIGURE 6.5. Cortical processing of spoken words. (A) Source localization using distributed modeling (minimum norm, MNE), left hemisphere displayed. The distribution of activation, plotted as a function of time from 100 to 1200 ms after stimulus onset, is an average over 10 subjects; noise-normalized MNEs of individual participants were morphed to a standard brain and normalized. A salient activation maximum persists in the superior temporal cortex. (B) ECD analysis reveals a functional substructure within the superior temporal maximum. Each dot represents the center of an active cortical patch in one subject and the line attached to it the mean direction of current flow in that area. There are two clusters of sources with practically orthogonal current flow and markedly different time courses of activation. Source-level activation strength is given in nanoamperemeters (nAm).

Source: Modified from Nora et al. (2012); Nora et al. (2015).

not be that surprising when participants are prepared to reproduce the heard word immediately afterward. However, the relevance of the motor cortex in speech perception has received much interest, and the possibility of directly testing whether the motor cortex might be active at an early or late stage of speech processing makes MEG an attractive tool for this type of research (Möttönen, van de Ven, & Watkins, 2014; Shtyrov, Butorina, Nikolaeva, & Stroganova, 2014). The robust N100m response, in particular, allows for fine distinctions in timing, on the order of milliseconds. In the later time windows, behaviorally relevant differences in timing may typically be identified in the range of tens to hundreds of milliseconds.

Word reading and picture naming activate the cortex much more widely than speech perception. Systematic stimulus manipulations have allowed associating part of these dynamics with specific processing stages. In word reading, the functionally identified sequence starts from stimulus-non-specific visual activation in the occipital cortex at ~100 ms, proceeds to letter-string analysis ~150 ms that is strongly lateralized to the left inferior occipitotemporal cortex, and then continues particularly to the left superior temporal cortex from ~200 ms onward, with the signal modulations associated with lexical-semantic, phonological, and even syntactic processing (Figure 6.6) (reviewed in Salmelin, 2007). This cortical representation of lexical-semantic processing is spatiotemporally remarkably similar for spoken and written words (Vartiainen, Parviainen, & Salmelin, 2009). The timing of the sustained left superior temporal response has been

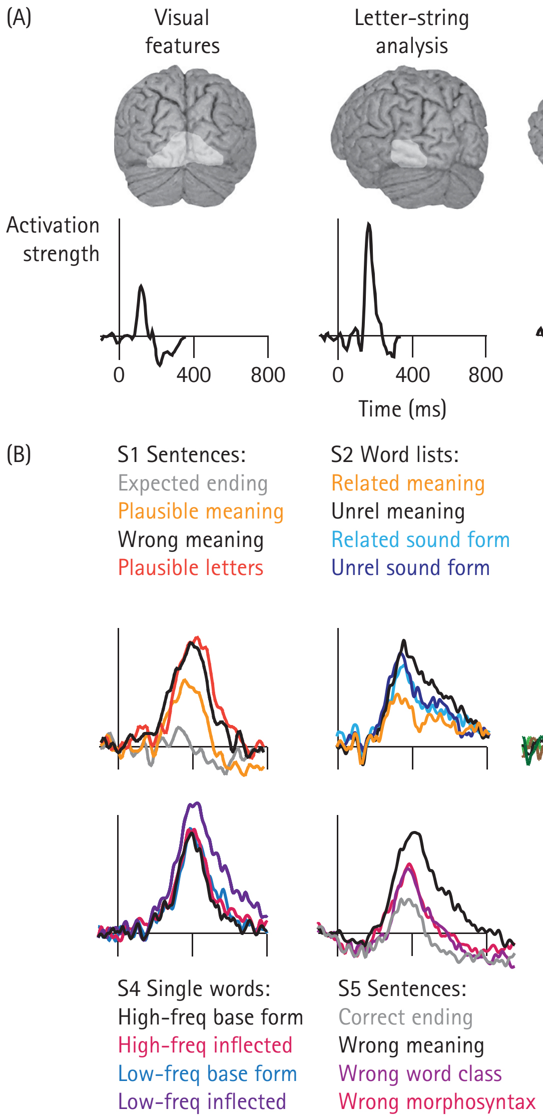


FIGURE 6.6. Cortical dynamics of word reading. (A) Among the extensive bilateral activation in reading, it is possible to identify three spatiotemporally and functionally highly consistent responses. Basic visual feature analysis is reflected in early, ~100-ms transient activation around the occipital midline. Letter-string activation occurs in the left inferior occipitotemporal cortex at ~150 ms. This stage reflects pre-lexical analysis, as the response is the same to words and nonwords, and even to consonant strings. The subsequent sustained activation in the left superior temporal cortex at 200 to 600 ms does differentiate between words and nonwords and reflects analysis of word meaning. (B) The left temporal sustained response seems to play a role in multiple types of processing, ranging from semantic and phonological analysis to morphosyntax. Examples from studies that used Finnish stimuli (agglutinative language with transparent orthography). *Study 1* (S1; Helenius et al., 1998) used sentences that created a very high expectation for a specific final word. The expected word suppressed the sustained response, whereas words

linked, for example, with the behavioral measure of reading speed (Helenius et al., 1998). An early ~100 ms activation of the left inferior frontal cortex (Broca's area) has additionally been reported in processing of English words and interpreted as fast phonological access in visual word recognition, possibly related to the contrived mapping between letters and sounds in the English language (Wheat, Cornelissen, Frost, & Hansen, 2010; Woodhead et al., 2014).

In picture naming, there is initial widespread activation in the occipital cortex within the first ~200 ms, and from about ~300 ms onward the activation advances to posterior temporal and frontal cortices (Levelt, Praamstra, Meyer, Helenius, & Salmelin, 1998; Liljeström, Hultén, Parkkonen, & Salmelin, 2009; Salmelin, Hari, Lounasmaa, & Sams, 1994; Vihla, Laine, & Salmelin, 2006). It has been fairly hard to associate specific cortical areas and time windows of cortical activation in picture naming with processing stages postulated by behaviorally based models. However, the left posterior temporal activation has been linked with both phonological and semantic processing, left frontal activation with output phonology, and the bilateral frontal activations with articulation (Hultén, Vihla, Laine, & Salmelin, 2009; Vihla et al., 2006).

Most often, MEG evoked responses are analyzed until the point of actual speech production and the nearly inevitable artifact signal from face and tongue muscles. It may be possible, although challenging, to markedly reduce the artifact and to track

FIGURE 6.6. Continued

with a wrong meaning and words with a wrong meaning but sharing the initial letters with the expected words (plausible letters) resulted in a strong response ("N400m"). The semantic gradation was manifested as the medium strong response to words that were not the expected words but had a plausible meaning in the sentence context. *Study 2* (S2; Vartiainen, Parviainen, & Salmelin, 2009) used lists of four words that were related either semantically or phonologically, and the final word either fulfilled the expectation set by the preceding three words (Related meaning/sound form) or not (Unrel meaning/sound form). Both modulations affected the response, but the semantic influence was markedly stronger. *Study 3* (S3; Wydell et al., 2003) examined cortical responses to short and long real words and pronounceable pseudowords (pseudow). The dual-route model of reading (Coltheart et al., 1993) predicts that the word length would have little influence on real word (lexical route) but a strong influence on pseudoword (grapheme-to-phoneme transformation) reading. Indeed, such an effect was found in the sustained response, suggesting a link to phonological analysis. *Study 4* (S4; Vartiainen, Aggujaro, et al., 2009) investigated reading of monomorphemic (base form) and inflected high- and low-frequency (high/low-freq) words. Only the low-frequency inflected words showed an increased processing cost (stronger activation), indicating that the sustained response also reflects morphosyntactic processing and that only very high-frequency inflected words are not parsed. *Study 5* (S5; Service et al., 2007) used sentences to explore morphosyntax. The strongest response was recorded to final words with a wrong meaning, while a correct ending resulted in a suppressed response. Notably, a medium strong response was elicited by endings where the correct word had the wrong inflectional form (wrong morphosyntax) or the expected noun was replaced by a verb (wrong word class).

Source: Modified from Helenius et al. (1998); Salmelin, Helenius, & Service (2000); Service et al. (2007); Vartiainen, Aggujaro, et al. (2009); Vartiainen, Parviainen, & Salmelin, (2009); Wydell et al. (2003).

the response all the way through the speech act (Salmelin, Schnitzler, et al., 2000; see also the discussion of artifactual signals earlier in this chapter), but the source-level model is certainly less reliable at that point. Small head movements due to speech are, however, less problematic than in fMRI: the spatially smooth electromagnetic field (discussed earlier in this chapter) can tolerate some movement without completely distorting the source-level model. MEG has helped to assess cortical correlates of phonetic, phonological, and word-level learning (Dobel et al., 2010; Hultén et al., 2014; Nora et al., 2012; Zhang et al., 2009). These studies have focused on the relative changes of the cortical responses to various types of stimuli (familiar, newly learned, unfamiliar).

Advancing from vocabulary learning to acquisition of syntax requires assessment of entire sentence structures. Figure 6.7 illustrates cortical areas involved in a task where participants, prompted by images of two animals, produced descriptive sentences of the type "bear begs mouse" using a newly learned artificial language (nouns, verbs, morphosyntactic rules) as well as their native Finnish language (Hultén et al., 2014). The MEG data highlighted the role of the right temporal cortex in a semi-naturalistic sentence-level task. This type of complex paradigm activates the cortex widely, with considerable inter-individual variation in the activation patterns. Applying both distributed, cortically constrained MNE and focal, spatially unconstrained ECD models can be very helpful in determining the regions that reflect neural activation, as well as in obtaining an estimate of how consistently a salient activation in or near a certain cortical region was observed in individual participants (Figure 6.7).

Evoked responses are an efficient tool when the experiment can be designed such that there are well-defined trigger points for averaging, and long enough intervals between triggers for reliable estimation of baseline. It is also possible to evaluate the effects of more continuous stimulation on specific cortical areas indirectly, using probe stimuli. For example, the stage of the auditory cortex has been probed by recording evoked responses to simple tone stimuli while the participant was reading silently or aloud (Numminen, Salmelin, & Hari, 1999). One may choose to extract additional information by evaluating the modulation of rhythmic activity (Laaksonen, Kujala, Hultén, Liljeström, & Salmelin, 2012; Salmelin, Helenius, & Service, 2000) or connectivity changes (Kujala et al., 2012). When the stimuli or tasks are temporally less precisely defined or continuous, rhythmic activity and connectivity are likely to be the tools of choice.

Cortical Rhythmic Activity Helps to Extend and Complement the View Provided by Evoked Responses

In neurolinguistics, most MEG studies have used evoked responses as a measure of neural engagement, with much fewer studies applying rhythmic activity. Generally, it seems that the two types of measures pick up rather different types of neural activity. Indeed, when both measures have been evaluated from the same cognitive data set (e.g., Laaksonen et al., 2012; Salmelin, Schnitzler, et al., 2000), they have provided quite

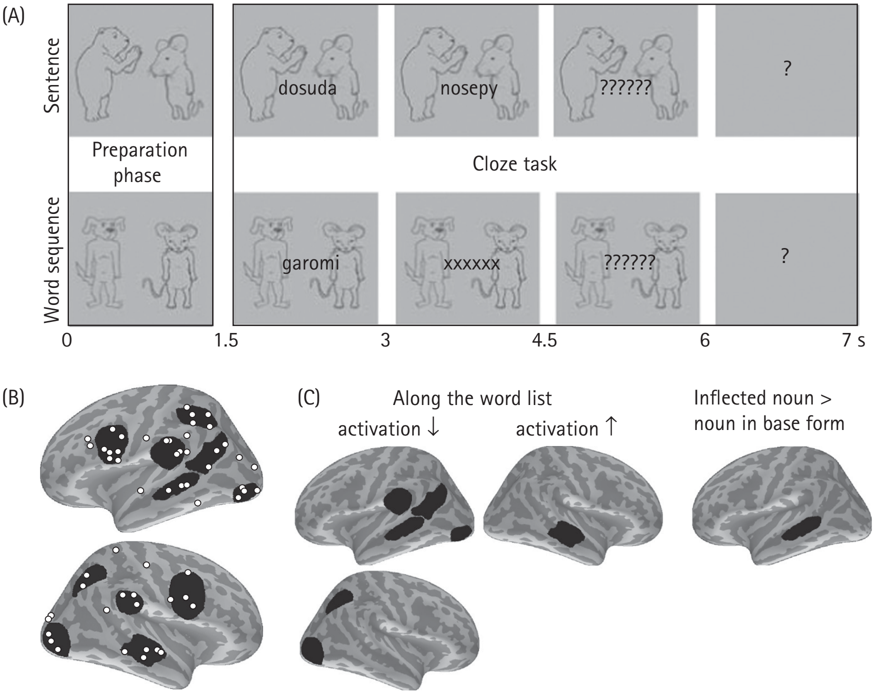


FIGURE 6.7. Sentence-level learning of vocabulary and grammar. A miniature language was created, called Anigram. It contains 20 nouns (animal names) and 10 transitive verbs, and has a subject-verb-object structure. The sentence object is indicated by a suffix, which is determined by the subject gender. (A) Example of the stimulus images. The image was first presented for 1.5 s, allowing the participants to plan the sentence. The more controlled cloze test part then started, where the words were printed on top of the picture, one by one, for 1.5 s each. Generation of the sentence object form was the most relevant test for grammar and word learning. A string of question marks prompted the participant to covertly produce the word form and then produce it overtly when the picture was replaced by a single question mark. As a control, Word sequence trials showed two animals standing next to each other, without a depicted action. The task was to retrieve the two animal names in their base form, without a syntactically controlled sentence structure. (B) Combining MNE and ECD modeling allowed the identification of MNE-derived group-level regional labels (black blobs) that represented real neural activity as they agreed with ECD (white dots) clustering across subjects. (C) The left and right temporal cortices displayed markedly different functions. In the left temporal cortex, activation was overall reduced when advancing along the word list (sentence or word sequence), but the response to the final word was stronger when it was inflected (sentence) than in the base form (word sequence). In contrast, in the right temporal cortex, activation was increased when advancing along the word list.

Source: Modified from Hultén et al. (2014).

complementary views of cortical implementation of language function. For example, when tested on multiple variants of a picture-naming paradigm, evoked responses and rhythmic modulation in the salient 10-Hz and 20-Hz bands yielded largely separate networks, with spatial overlap mainly in the primary sensorimotor and visual areas. Moreover, in the cortical regions that were identified with both measures, the experimental effects that each measure conveyed differed in terms of timing and function (Laaksonen et al., 2012).

Similar to evoked responses as the workhorse of noninvasive electromagnetic mapping, modulation in the gamma-band activity has assumed the corresponding role in intracranial recordings (electrocorticography, ECoG). It is thought to pinpoint the functionally most interesting cortical phenomena (Lachaux, Axmacher, Mormann, Halgren, & Crone, 2012) and has been proposed as the most direct counterpart of the blood oxygenation level dependent (BOLD) fMRI signal (McDonald et al., 2010; see Heim & Specht, Chapter 4 in this volume). With MEG, gamma activity can be quite salient in the visual cortex (Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006) but often is less conspicuous in other areas. Nevertheless, gamma activity has also been reported with MEG in areas other than the visual cortex (Lehongre, Ramus, Villiermet, Schwartz, & Giraud, 2011; van Ackeren, Schneider, Musch, & Rueschemeyer, 2014), especially when its SNR has been enhanced through correlation between frequencies (Gross, Hoogenboom, et al., 2013; Holz, Glennon, Prendergast, & Sauseng, 2010), areas (Betti et al., 2013; Kujala et al., 2012) or different imaging measures (Kujala et al., 2014).

Event-related modulations of the lower, more salient frequency bands have been informative in MEG studies of language (Arnal, Wyart, & Giraud, 2011; Bastiaansen, Magyari, & Hagoort, 2010; Longcamp, Tanskanen, & Hari, 2006). For example, motor cortex involvement in speech production has been tracked with the help of 20-Hz modulation, as the muscle artifacts can be less problematic in that frequency band than at frequencies below 10 Hz or in the gamma range or when using evoked responses. Such studies have shown, for example, an active role for the motor cortex in cognitive control of visually triggered mouth movements beyond mere movement execution, left-hemisphere precedence for control of mouth movements, and clear focus to the face/mouth area in linguistic mouth movements but involvement of the neighboring hand representation area in nonlinguistic mouth movements (Saarinen, Laaksonen, Parviainen, & Salmelin, 2006; Salmelin & Sams, 2002). In speech perception, cortical rhythmic activity is often utilized in a rather different manner, by focusing on coupling between the speech input and the time course of auditory cortical activation, as well as cross-frequency coupling within the auditory cortex. Such studies have found, for example, that the listener's auditory cortex tracks the speaker's prosodic rhythm (Bourguignon et al., 2013), the theta band (~5 Hz) tracks and discriminates spoken sentences (Luo & Poeppel, 2007), the cerebro-acoustic phase locking is strongest for intelligible speech (Peelle, Gross, & Davis, 2013), and coupling between theta and gamma oscillations plays an important role in the segmentation and coding of speech (Gross, Hoogenboom, et al., 2013).

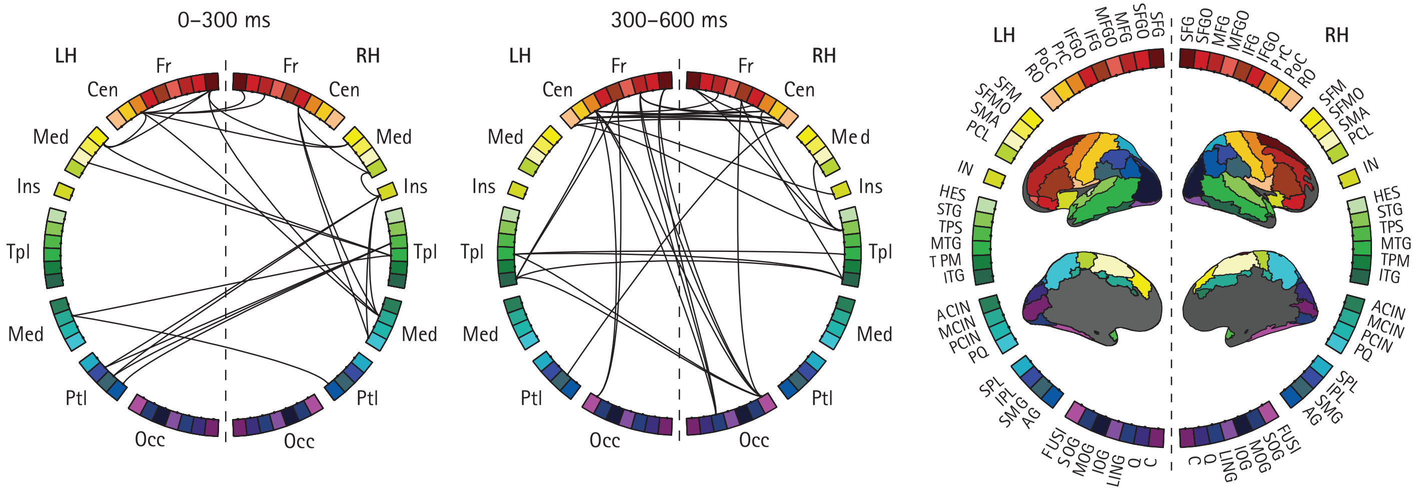
Connectivity Measures Can Reveal Networks That Support Language Processing

Connectivity analysis is being increasingly applied to language function, both in form of EMG–MEG coherence estimation and as full-fledged all-to-all cortico-cortical connectivity computation. For example, it has been demonstrated that during articulation, coherent oscillatory coupling between the mouth sensorimotor cortex and the mouth muscles is strongest at the frequency of the individual spontaneous rhythmicity of speech at 2–3 Hz, which is also the typical rate of word production (Ruspantini et al., 2012). During writing, EMG–MEG coherence was found to appear primarily in the frequency of writing movements (3–7 Hz) while MEG–MEG coherence between cerebral sources occurred at ~10 Hz (Butz et al., 2006). Direct cortico-cortical coherence estimation applied to reading (rapid serial visual presentation of connected text) also identified ~10 Hz as the dominant frequency of cortico-cortical interaction. When Granger causality was evaluated among the most densely connected cortical areas, the left inferior occipitotemporal cortex, involved in early letter-string processing, and the cerebellum turned out to be the main forward driving nodes of the network (Kujala et al., 2007). It is also possible to track the evolution of connectivity in an event-related design, with reasonable temporal specificity (~300 ms), as illustrated by comparison of coherence maps over the course of silent versus overt picture naming (Figure 6.8) (Liljeström et al., 2015).

Language Processing Can Be Studied in the Developing Brain

The spatiotemporal dynamics accessible with MEG can provide interesting insights to the development of the cortical correlates of language. MEG recordings are safe and completely noninvasive. In addition, the noiseless environment is more pleasant than the noisy and confined MR environment, which is an important advantage when studying young children. As long as the participants can stay reasonably well in place, which tends to be the case for small babies and children older than about 7 years, MEG recordings are technically feasible (Huotilainen, Shestakova, & Hukki, 2008; Kuhl, Ramirez, Bosseler, Lin, & Imada, 2014; Parviainen, Helenius, Poskiparta, Niemi, & Salmelin, 2011), particularly when the head position within the helmet can be recorded continuously. MEG has been used to follow the development of the auditory system in discriminating speech sounds in newborns and infants from 6 months of age (Huotilainen et al., 2008; Kuhl et al., 2014), permitting the identification and separation of cortical sources in auditory versus motor regions (Kuhl et al., 2014).

MEG can also be utilized to compare both spatial and temporal characteristics of neural activation between children and adults (Kuhl et al., 2014; Parviainen et al., 2011). Figure 6.9 illustrates the time course of activation in word reading in 7- to 8-year-old children, compared with the adult time course (Parviainen, Helenius, Poskiparta, Niemi, & Salmelin, 2006). Although these children were still fairly fragile readers, the overall sequence of activation was qualitatively quite similar to that in adults: stimulus-non-specific visual activation in the occipital cortex followed by a transient letter-string activation in the left inferior occipitotemporal cortex and sustained activation in the left superior temporal cortex. However, the activation was significantly delayed in children, by ~50 ms in the first stage of low-level visual analysis, by ~100 ms


0–300 ms
300–600 ms
LH
RH
Fr
Cen
Med
Ins
Tpl
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SFG
SFGO
MFG
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IFG
IFGO
PrC
PoC
RO
SFM
SFMO
SMA
PCL
IN
HES
STG
TPS
MTG
TPM
ITG
ACIN
MCIN
PCIN
PQ
SPL
IPL
SMG
AG
FUSI
SOG
MOG
IOG
LING
Q
C

SFG	Superior frontal gyrus, dorsolateral
SFGO	Sup. frontal gyrus, orbital part
MFG	Middle frontal gyrus
MFGO	Mid. frontal gyrus, orb. part
IFG	Inferior frontal gyrus
IFGO	Inf. frontal gyrus, orb. part
PrC	Precentral gyrus
PoC	Postcentral gyrus
RO	Rolandic operculum
SFM	Sup. frontal gyrus, medial
SFMO	Sup. frontal gyrus, medial orbital
SMA	Supplementary motor area
PCL	Paracentral lobule
IN	Insula
HES	Heschl gyrus
STG	Superior temporal gyrus
TPS	Temporal pole, sup. temp. gyrus
MTG	Middle temporal gyrus
TPM	Temporal pole, mid. temp. gyrus
ITG	Inferior temporal gyrus
ACIN	Anterior cingulate gyrus
MCIN	Middle cingulate gyrus
PCIN	Posterior cingulate gyrus
PQ	Precuneus
SPL	Superior parietal lobule
IPL	Inferior parietal lobule
SMG	Supramarginal gyrus
AG	Angular gyrus
FUSI	Fusiform gyrus
SOG	Superior occipital gyrus
MOG	Middle occipital gyrus
IOG	Inferior occipital gyrus
LING	Lingual gyrus
Q	Cuneus
C	Calcarine fissure and surrounding cortex

FIGURE 6.8. Task-dependent modulation of coherence in cortical networks in picture naming. Connectivity circles at 0–300 ms (*left*) and 300–600 ms (*middle*), with respect to the onset of the pictured item, indicate which areas of the parcellated cortex (*right*) were more coherently active when preparing for overt naming than for naming silently. Pooled across frequencies 3–90 Hz.

Fr = frontal, Cen = central, Med = medial, Ins = insular, Tpl = temporal, Ptl = parietal, Occ = occipital.

Source: Modified from Liljeström et al. (2015).

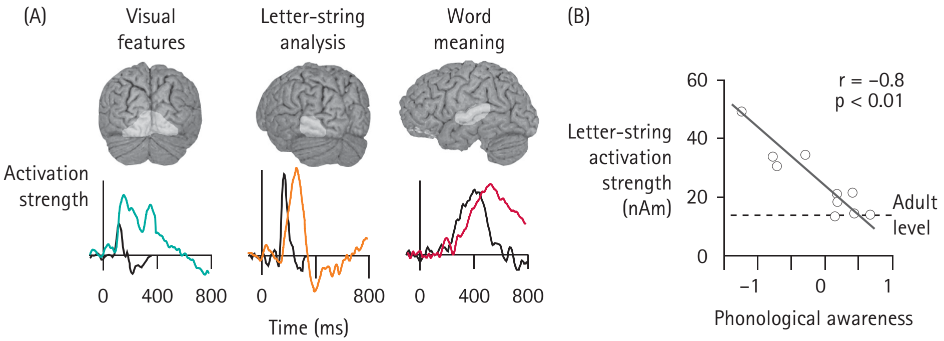

FIGURE 6.9. Development of language function. (A) Cortical dynamics of silent reading in seven- to eight-year-old children (colored curves) and in fluently reading adults (black curves). In children, the sequence of activation was qualitatively similar to that in adults but delayed in time. (B) A letter-string-sensitive response was detected in about half of the children. Those children showed a strong correlation between phonological awareness, estimated with a set of behavioral tests, and the cortical activation strength. The response strength was decreased with better phonological skills, approaching the adult level of activation, which is generally much lower than in children.

Source: Modified from Parviainen et al. (2006).

at the stage of letter-string processing, and even more by the sustained superior temporal response reflecting lexical-semantic processing. The somewhat larger variability of response timing in children than adults further allowed the demonstration of significant correlation between the timing of the stages of visual and letter-string processing, on the one hand, and the letter-string and semantic processing, on the other hand. The strength of the letter-string response in children correlated with their behaviorally estimated phonological abilities.

Language Lateralization and Disorders May Be Assessed with MEG

MEG serves as a clinical tool, and it is widely used to identify brain sources of epileptic spikes, to map sensorimotor cortex prior to brain surgery, and to assess the brain effects of stroke. As regards language processing in the clinical context, the aspect that is being most fervently addressed is that of language lateralization, with MEG as a means to replace the highly invasive Wada test, possibly combined with other imaging measures (Kamada et al., 2007). Proposed approaches include counting the number of localizable ECDs in the left and right hemisphere when participants see or hear words (Papanicolaou et al., 2004; Tanaka et al., 2013), evaluation of the spatial sensitivity of activation maps (D'Arcy et al., 2013), estimation of beta-band power modulations (Findlay et al., 2012), and comparison of auditory-cortex N100m responses to vowels versus tones (Kirveskari, Salmelin, & Hari, 2006).

When characterizing aphasia, it can be particularly important to collect data from two separate sessions, as there may be far more day-to-day variation in a damaged brain than in a healthy one, partly due to emergence of low-frequency activity (Laine, Salmelin, Helenius, & Marttila, 2000). MEG studies have shown, for example, that the generally remarkably similar cortical dynamics of action versus object naming from the same images in healthy controls were markedly dissociated in an aphasic patient with specific difficulties with noun naming (Sörös, Cornelissen, Laine, & Salmelin, 2003); that effortful reprocessing of perceived sentences in short-term memory can support improved comprehension in aphasia (Meltzer, Wagage, Ryder, Solomon, & Braun, 2013); and that successful treatment of word-finding difficulties in aphasia can strengthen activation related to picture naming in the damaged left hemisphere (Cornelissen et al., 2003).

The excellent time resolution of MEG has proven valuable particularly when studying how individuals with developmental language disorders perform in linguistic tasks. When reading-impaired adults are compared with non-reading-impaired controls, the cortical responses within the first ~200 ms after spoken or written word presentation differ in activation strength, but from ~200 ms onward, in timing: in reading-impaired individuals, the cortical response reflecting lexical-semantic processing is delayed both in speech perception (~50 ms) and reading (~100 ms) (Helenius, Salmelin, Service, & Connolly, 1999; Helenius et al., 2002). In developmental stuttering, functionally important timing differences appear in speech preparation, outside of the core language processes (Figure 6.10): in fluent speakers, the left inferior frontal cortex was found to be activated first, followed by left motor/premotor cortex, but in the stutterers the order was reversed, thus suggesting that motor preparation started prior to articulatory planning (Salmelin, Schnitzler, et al., 2000).

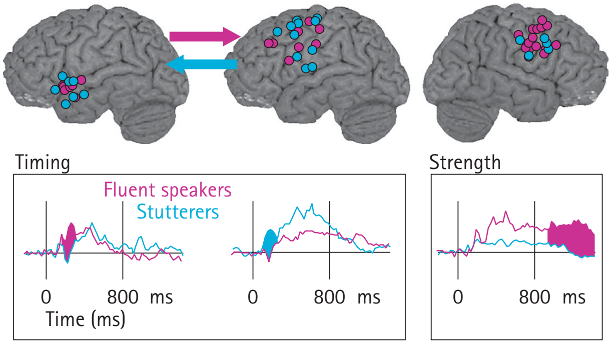

FIGURE 6.10. Altered cortical dynamics in stuttering. Source areas in which differences were found between groups of fluent speakers and stutterers, with the time courses of activation depicted below. Differences in timing were found within 400 ms after word presentation and differences in activation strength at the time of overt speech production.

Source: Reproduced from Salmelin (2010).

New Winds: How MEG May Further Contribute to a Better Understanding of Language Function

New Devices May Increase the Spatial Accuracy of MEG

In the current MEG systems, the sensors are located at least 3 cm away from even the most superficial neural current sources. This is because the need to keep the superconducting sensors in a low-temperature bath of liquid helium necessitates a rigid structure and insulated outmost layer of the MEG helmet. The helmet, with its fixed sensor array, provides an excellent coverage for much of the cortex, but less optimal coverage especially for the most anterior and inferior parts of the frontal and temporal cortices. The considerable gap between sensors and sources is unfortunate, as the magnetic field dies away rapidly with distance.

In the future, novel room-temperature sensor designs, such as atomic magnetometers (Dang, Maloof, & Romalis, 2010; Mhaskar, Knappe, & Kitching, 2012), will likely allow bringing the sensors closer to the head and setting up a more extensive coverage of the cortex. Thus, they propose to markedly improve the spatial resolution of MEG and allow better dissociation of the contribution from nearby cortical regions. In fact, it is possible that devices based on these principles would eventually facilitate whole-head MEG recordings with comparable sensitivity and specificity (at least in cortical regions) to those obtained with intracranial EEG recordings. For example, gamma activity, thought to reflect highly local signaling (Buzsaki & Wang, 2012) and not readily picked up at the distance available with the current MEG systems, might become better detectable with the new sensors. Such new MEG devices would allow the tracking of language processing with a combined spatial and temporal specificity that is not currently possible, even with joint use of different neuroimaging modalities.

Task-Related Connectivity Can Be Tracked as a Function of Time

During the last decade, the vast majority of interaction studies have focused on resting-state connectivity. Whether such studies have used MEG or fMRI, they generally have ignored the modulation of connectivity across time. Recently, new interest has arisen in the nonstationarity of connectivity during rest, as well as during and between different task conditions. These are questions that can be addressed best with MEG and its superior temporal resolution compared with, for example, fMRI. So far, the temporal resolution of MEG has been utilized implicitly, by focusing on oscillatory neurophysiological mechanisms of interactions (Palva & Palva, 2012).

It is now also possible to explicitly evaluate the specific times at which connectivity modulations manifest or experimental conditions differ from each other. For example, it has been shown that network-level modulations occur at different times in semantic and phonological priming of written words (Kujala et al., 2012). Moreover, it has been demonstrated in picture naming that the additional cortical connectivity in overt versus silent naming is not stationary but changes markedly from the early to late time window preceding speech (cf. Figure 6.8) (Liljeström et al., 2015). MEG thus allows researchers to follow the dynamic reconfiguration of the interacting cortical networks at the scale of hundreds of milliseconds as the tasks unfold. Such a capacity offers the possibility not only to determine the relevant network structures but also to dissociate between early and late network interactions and thus, presumably, lower- and higher-level distributed processing in language perception and production.

Multiple Distinct Imaging Views and Genetic and Behavioral Measures Will Be Combined for a More Complete Picture of Human Language Function

Currently, most MEG studies focus on one measure of choice. However, as evoked responses, modulation of cortical rhythms, and connectivity measures each provide their own angles to the study of brain function, it would seem worthwhile to exploit such complementary information in the future. Some recent studies have sought to do just that. A study of semantic and phonological priming of written words found that while activation was reduced in the same area and time window (superior temporal cortex at 250–650 ms) for both types of priming, the spatiospectral connectivity patterns differed between the two processes (Kujala et al., 2012). Other studies have utilized both evoked responses and modulation of rhythmic activity to characterize language comprehension (Wang et al., 2012) and cortical effects of the age of acquisition on object recognition (Urooj et al., 2014).

Even more angles to the cortical correlates of language function can be obtained by combining different imaging modalities. Electrophysiological imaging with MEG and hemodynamic imaging with fMRI form an interesting combination, as functional localization can be done readily and independently with each method, and the results may then be considered together. Such multimodal imaging has been applied to speech processing (Renvall, Formisano, et al., 2012), reading (Lau, Gramfort, Hämäläinen, & Kuperberg, 2013; McDonald et al., 2010; Vartiainen, Liljeström, Koskinen, Renvall, & Salmelin, 2011) and picture naming (Liljeström et al., 2009). While the methods have converged on a number of functional interpretations, they have also indicated some salient differences, particularly in word reading (Vartiainen et al., 2011): Semantic processing was associated with the left inferior frontal cortex in fMRI, as usual, but with the left superior temporal cortex in MEG, again as usual. Perhaps even more intriguingly, the MEG-fMRI data, combined with a host of earlier, separate MEG and fMRI literature, indicated that the MEG evoked response to letter-strings in the left occipitotemporal cortex reflects largely a feed-forward process, as it is not influenced by task. The corresponding BOLD fMRI signal, however, was strongly affected by task, suggesting considerable feedback influence. The possibility that MEG and fMRI might be differentially sensitive to feed-forward versus feedback processes should be worth exploring, as it represents an essential step toward an informed use of multimodal imaging that would reach beyond the mere combination of location and timing of neural activation.

In striving for a more complete picture of language processing, behavioral and other non-brain measures, such as eye tracking, should obviously be incorporated into the analysis as much as possible, while retaining the MEG signals as noise-free as possible. Research into the influence of genes on the MEG responses, let alone on the complex linguistic activations, is only starting but will likely become an important component of understanding human language processing, its cortical correlates, and their individual variation. There are two main approaches: choose a gene and test the effect of its haplotypes on cortical measures (Lamminmäki, Massinen, Nopola-Hemmi, Kere, & Hari, 2012), or find a cortical signal with suitable properties (robust within an individual, comparable between siblings, and highly variable across non-siblings) and perform a genome-wide search for genes that influence that response (Renvall, Salmela, et al., 2012).

Multivariate Analysis and Predictive Computational Models Promise a New Angle to Assessing Cortical Implementation of Language

To date, most MEG studies have focused on univariate analysis and have compared different stimulus categories (e.g., words vs. nonwords, verbs vs. nouns, speech vs. nonspeech sounds, related vs. unrelated items), tasks (e.g., overt vs. covert naming, semantic vs. perceptual decisions), or participant groups (e.g., adults vs. children, reading-impaired vs. control participants). Over the recent years, multivariate analyses and computational techniques derived from machine learning have also found their way into MEG studies of language (Chan, Halgren, Marinkovic, & Cash, 2011; Clarke, Devereux, Randall, & Tyler, 2015; Koskinen et al., 2013; Miozzo, Pulvermuller, & Hauk, 2015; Simanova, van Gerven, Oostenveld, & Hagoort, 2015; Sudre et al., 2012).

The cortical representation of individual word meanings and the time course of word processing from primarily perceptual to essentially semantic features have been of particular interest (Chan et al., 2011; Clarke et al., 2015; Sudre et al., 2012); word categories have been classified even in a free word-generation task (Simanova et al., 2015). Generative computational models have further allowed researchers not merely to distinguish between the individual item maps, but also to estimate the cortical dynamics of the possible underlying features, ranging from low-level visual properties such as aspect ratio (visual cortex, 0–200 ms) to high-level cognitive properties such as whether one can hold the item (superior parietal cortex, 200–400 ms) or whether the item is bigger than a car (sensorimotor cortex, 400–600 ms) (Sudre et al., 2012). While the new tools make it possible to work on the item level instead of stimulus categories, multiple trials per item (or multiple items per category when classifying by category) are still needed to ensure a reasonable SNR. However, whether the reasonable minimum number will turn out to be 5, 10, or 20, it seems that a markedly lower number of trials per item may suffice than in the more traditional univariate analysis.

In conclusion, MEG combines millisecond-level timing with reasonable spatial accuracy and is, therefore, an excellent method for tracking the cortical dynamics of language processing. Language, as a higher cognitive function, seems to rely largely on cortical activation, and that is what MEG detects best. After 20 years of research with helmet-like sensor systems that, by covering the whole head at once, truly facilitated MEG study of higher cognitive functions, we have a good basic understanding of the cortical dynamics of speech perception, reading, and picture naming (speech production) as measured by evoked responses. We can now build on this solid basis when learning to make the best, most informative use of the various neuroimaging measures in the study of cognition and aiming to deepen our understanding of the organization of language and knowledge in the human brain.

Acknowledgments

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CHAPTER 7

SHEDDING LIGHT ON LANGUAGE FUNCTION AND ITS DEVELOPMENT WITH OPTICAL BRAIN IMAGING

YASUYO MINAGAWA AND ALEJANDRINA CRISTIA

INTRODUCTION

NEAR-INFRARED spectroscopy (NIRS) measures local changes in the concentrations of oxygenated (oxy-) and deoxygenated (deoxy-) hemoglobin (Hb) associated with regional activation in the cerebral cortex, similar to magnetic resonance imaging (MRI) (see Heim & Specht, Chapter 4 in this volume). NIRS is portable, innocuous, noninvasive, and relatively resistant to movement artifacts, which makes it ideal for use with vulnerable and/or mobile populations (e.g., awake infants and children; Cristia et al., 2013). Although electroencephalography (EEG) (see Leckey & Federmeier, Chapter 3 in this volume) shares several of these advantages, the superior spatial resolution of NIRS invites examination of localization questions. The introduction of multi-channel NIRS in the early 1990s led to the development of the technique as a means of measuring human cognitive functions, sometimes referred to as functional NIRS (fNIRS) (Hoshi & Tamura, 1993; Kato, Kamei, Takashima, & Ozaki, 1993; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993). Since then, more than 1,200 papers with a use of NIRS, including language studies, have been published (Boas, Elwell, Ferrari, & Taga, 2014). These language studies include some with clinical populations such as cochlear-implanted individuals, people diagnosed with schizophrenia, people with a diagnosis of a developmental disorder (including autism spectrum disorder and stuttering, among others), and others investigating general language function in normal adults.

This chapter first illustrates the general principles of NIRS and outlines its pros and cons by comparing it with other brain-imaging methods with a view of the optimal investigation of language. We then summarize the general methodological aspects of NIRS, including experimental paradigms, procedures, and data analyses. These sections are partly based on previous articles (Minagawa-Kawai, Mori, Hebden, & Dupoux, 2008; Minagawa-Kawai et al., 2009). Functional neuroimaging is an interdisciplinary area where knowledge of physiology, engineering, psychology, and information processing are required. These sections describe these components in a comprehensible fashion. NIRS has many aspects in common with functional magnetic resonance imaging (fMRI). Thus, these method sections would be helpful to students or beginners of fNIRS as well as fMRI. Finally, we review some of the neurolinguistic discoveries made so far in this emerging research field.

FUNDAMENTALS OF THE NIRS SYSTEM: HOW NIRS MEASURES BRAIN ACTIVITY

General Principles

Electrophysiological and hemodynamic measures are the two brain signals that have mainly been utilized in neuroscience. NIRS measures the latter type of signal as changes in oxy- and deoxy-Hb provide an indirect indication of cerebral activities. Brain activation is closely related to regional changes in blood flow and oxygenation (Fox & Raichle, 1986). Despite the unclear relationship between neuronal activity and the vascular response (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), studies on hemodynamic behavior in the brain are based on the assumption that an increase in blood flow, which in turn causes an increase in the mean local oxygenation, signals an increase in brain activity. Blood flow and blood volume are correlated and are mostly interchangeable when assessing cerebral activity with some reasonable assumptions (K. Villringer et al., 1997; Hoshi, Kobayashi, & Tamura, 2001; Strangman, Culver, Thompson, & Boas, 2002).

NIRS evaluates brain function by identifying changes in the concentrations of oxy- and deoxy-Hb in the circulating red blood cells by measuring changes in the diffuse transmittance of NIR light at a suitable combination of wavelengths. Their specific absorption coefficients are shown in Figure 7.1. Notice that at around 800 nm the coefficients of the two types of Hb are equal. Usually researchers measure a few wavelength points (e.g., one under 800 nm and the other above 800 nm), so as to accurately estimate changes in oxy-Hb and deoxy-Hb concentrations separately, and additional ones for other chromophores such as cytochrome. A chromophore is a functional group of molecules responsible for color, namely wavelength. Chromophores have different light absorption characteristics, which can therefore be measured using optical measurements. Further details of the principles of NIRS are described by Ferrari, Mottola, and Quaresima (2004).

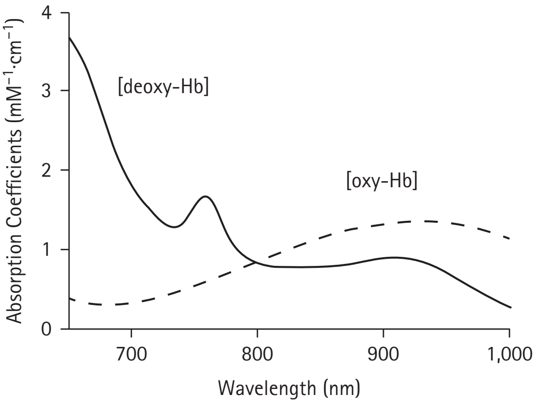

FIGURE 7.1. NIR absorption spectra of oxygenated hemoglobin [oxy-Hb] and deoxygenated hemoglobin [deoxy-Hb].

The Continuous-Wave System among Various NIRS Systems

There is a variety of methods and instruments proposed for noninvasive NIRS, including time-domain systems, frequency-domain systems, and continuous-wave (CW) systems. Further, using particular techniques, these systems can enable us to map the activation in either a two-dimensional or a three-dimensional fashion, as illustrated in Figure 7.2. The most common and simplest method involves measuring the intensity of diffusely reflected light using continuously emitting light sources. Instruments capable of performing such measurements are referred to as CW (continuous-wave) systems, and multichannel CW NIRS is now largely used for functional neuroimaging, namely fNIRS. Many of the cognitive studies, including language studies, have been carried out with CW fNIRS. Henceforth, when we speak of fNIRS, we will refer to CW unless otherwise noted. As for other systems, readers can find a summary of each system in the next section.

In CW systems, at least once source is placed in a given location on the scalp. One or multiple detectors are then placed at a certain distance, and the intensity of the light as it has traveled from the source to the detector(s) is measured (see Figure 7.2). Notice that, in this flight through not only the cerebral cortex (of most interest) but also the skull and skin and so on, the light is highly scattered and attenuated. With sufficient separation of source and detector fibers, a significant proportion of the detected signal penetrates the cortical regions of the brain (Okada & Delpy, 2003). Changes in the intensity at two or more wavelengths can then be converted into changes in concentrations of oxy-Hb and deoxy-Hb using the modified Beer-Lambert law (Reynolds et al., 1988; Delpy & Cope, 1997). The modified Beer-Lambert law is expressed as

$$A = \log_e\left(I_0/I\right) = \varepsilon \times c \times d \times \mathrm{DPF} + G \qquad (7.1)$$

where A is the attenuation, I_0 and I are the initial and final intensities, ε is the specific extinction coefficient of the chromophore (measured, for instance, in μmolar^{-1}. cm^{-1}), *c* is the concentration of the chromophore (which may be expressed in μmolar units), *d* is the distance between the source and detector fibers, DPF is a differential path length factor, and G is an unknown term due to scattering losses. DPF is the ratio of the mean path traveled in the tissue by detected photons (elementary particles of light) and the minimum path *d*. Although path length does not vary by more than ~10% due to intra-individual variability across different brain areas and about ~20% due to inter-individual variability (Ferrari, Wei, Carraresi, De Blasi, & Zaccanti, 1992; Duncan et al. 1996), the exact value of DPF remains unknown because light does not travel in a straight light. Since neither G nor DPF is known, the absolute change in the chromophore concentration cannot be derived. However, if we consider *changes* in attenuation due to *changes* in the concentrations of oxy-Hb and deoxy-Hb, we can eliminate G as follows:

$$\Delta A = \{\, \Delta c[\text{oxy Hb}] \times \varepsilon[\text{oxy Hb}] + \Delta c[\text{deoxy Hb}] \times \varepsilon[\text{deoxy Hb}]\} \times d \times \text{DPF} \qquad (7.2)$$

If measurements of ΔA are determined at *two wavelengths* (e.g., 780 nm and 830 nm), simultaneous equations can be obtained and solved for Δc[oxy-Hb] and Δc[deoxy-Hb], estimating an appropriate value for DPF. These values can then be used to calculate changes in blood volume and oxygenation. Although the absolute Hb concentration changes cannot be derived with the CW system as explained, some other systems are capable of this, as described in the next section. Other limitations of CW NIRS are illustrated elsewhere (Obrig & Villringer, 2003; Scholkmann et al., 2014).

The technique known as optical topography (Watanabe, Yamashita, Maki, Ito, & Koizumi, 1996), or multi-channel NIRS, uses arrays of multiple NIR sources (e.g., laser diodes) and detectors (Figures 7.2, 7.3). This method enables a broad area of the cortex to be sampled with minimal numbers of optical fibers, and a two-dimensional

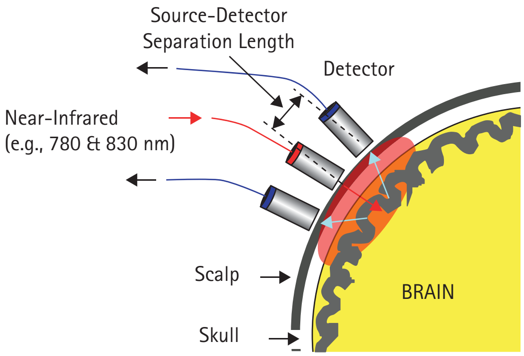

FIGURE 7.2. Optical topography using an array of sources and detectors. Near-infrared light illuminates the brain through the skin and skull, and is diffusely reflected back toward the detectors.

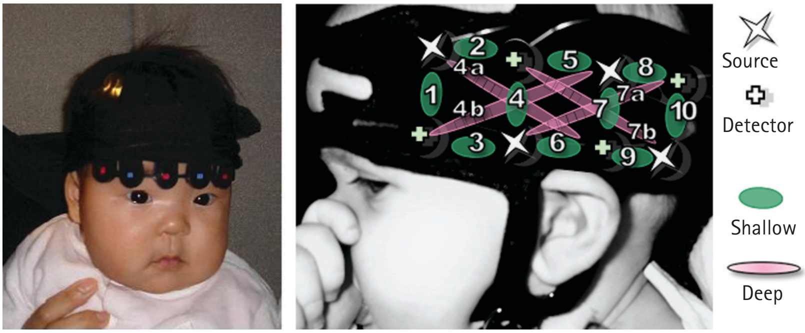

FIGURE 7.3. A NIRS measurements of (*left*) frontal cortex in a 3-month-old infant using a Hitachi CW optical topography system; (*right*) temporal cortex in an infant using the UCL optical topography system.

map of brain activity to be generated. In order to identify the source associated with a given detected signal, it is necessary to either illuminate each source sequentially or modulate each source at a unique frequency, following which the signals can be distinguished using lock-in amplifiers or software to calculate the Fourier transform. Several CW optical topography systems have been developed and employed to study the human cognitive function (Chance et al., 1998; Hintz et al., 2001; Koizumi et al., 2003).

Other Systems

Time-Domain Topography

The obstacle that prevents CW NIRS from obtaining absolute chromophore concentrations is the unknown DPF (DPF in equations (7.1) and (7.2)) due to the fact that NIR light does not travel through tissue in a straight line. In order to evaluate changes in chromophore concentration in nonarbitrary units, we should determine the average path length of the diffusely reflected light (i.e., to determine an average value of $d \times$ DPF in equation (7.2)). A time-domain system can directly record the path length using a short laser pulse and a fast time-resolved detector. The average flight time multiplied by the speed of light through the tissue provides the mean path length. A time-domain system utilizes this principle (Delpy et al., 1988), usually using time-correlated single-photon counting hardware. These systems necessitate longer acquisition times (as single photons need to be tracked accurately) but have the advantage of providing better resolution, both in terms of localization and in terms of the separate estimation of absorption and scatter (Arridge & Lionheart, 1998). Although time-domain devices are not normally used for fNIRS studies at present, this has a large potential to be a first choice of fNIRS with further development (Torricelli et al., 2014).

Frequency-Domain System

The average path length can also be calculated using an intensity-modulated source and a device that measures the phase delay of the transmitted signal (Chance, Maris, Sorge, & Zhang, 1990). This method is employed by NIRS with frequency-domain systems. Such systems do not rely on photon counting, and therefore provide greater signal-to-noise ratio (SNR) and dynamic range than time-domain systems. However, they provide less adequate temporal information unless multiple frequencies are employed (Nissila et al., 2006).

Apart from identifying hemodynamic changes in the brain, optical techniques can detect signals considered to be of neuronal origin that vary over much smaller time intervals. The neuronal signal exhibits a latency of around 10–100 milliseconds (ms), and changes in neuronal tissue scattering have been proposed as a possible cause of this signal (Franceschini & Boas, 2004; Gratton & Fabiani, 2001; Gratton, Sarno, Maclin, Corballis, & Fabiani, 2000). Therefore, this may provide much more direct measures of cellular activity. This method is sometimes called event-related optical signal (EROS) or fast NIRS. At present, this technique is also limited to measurements of the cortical surface area. Although this technique is well established for invasive NIRS with exposed brains, noninvasive fast NIRS (e.g., Gratton & Fabiani, 2001) has not been sufficiently studied (Steinbrink et al., 2000; Steinbrink, Kempf, Villringer, & Obrig, 2005) and may require further examination for effective general use.

Tomography System

If there is a sufficient number of sources and detectors within a probe pad, it is feasible to use NIRS measurements to generate three-dimensional images of the optical properties within the brain (for a review, see Gibson, Hebden, & Arridge, 2005). Although this type of system is still being developed to improve its resolution and accuracy, diffuse optical tomography (DOT) has already shown a functional mapping of visual cortex with millimeter-order spatial resolution for both activation and functional connectivity during visuo-motor coordination (Zeff, White, Dehghani, Schlaggar, & Culver, 2007; White et al., 2009). This is a promising tool to study human language function in the future.

GENERAL CHARACTERISTICS OF NIRS WITH A VIEW TO NEUROLINGUISTIC RESEARCH

Hemodynamic Physiology

One of the strong advantages of NIRS is its ability to measure both oxy-Hb and deoxy-Hb (and consequently also total Hb), whereas blood oxygenation level dependent

(BOLD) fMRI is sensitive only to changes in the ratio of oxy- to deoxy-Hb. Thus, NIRS provides rich signal information on neural activation. Indeed, studies using NIRS have shown that an absence of a BOLD signal does not always indicate a lack of brain activation (Fujiwara et al., 2004; Seiyama et al., 2004). An increase in local arterial blood flow produces an increase in oxy-Hb and a decrease in deoxy-Hb, whereas an increase in oxygen consumption causes a decrease in oxy-Hb and an increase in deoxy-Hb. Previous NIRS studies have reported that the overall effect of these opposing mechanisms is different in infants than in adults, possibly due to the immaturity of vascular regulation. Whereas brain activation in adults usually causes a localized increase in oxy-Hb and a decrease in deoxy-Hb, known as the hemodynamic response function (HRF) (A. Villringer et al., 1993; also see Sakatani, Xie, Lichty, Li, & Zuo, 1998), some infant data are consistent with a net increase in both oxy-Hb and deoxy-Hb (e.g., Meek et al., 1998; Sakatani, Chen, Lichty, Zuo, & Wang, 1999). Another atypical variation involves a decrease in oxy-Hb and increase in deoxy-Hb for 4-month-olds (Csibra et al., 2004) and 1- to 3-month-olds (Kusaka et al., 2004). These atypical HRF patterns have been chiefly reported for the occipital cortex in response to visual stimuli, and only rarely for the sensorimotor area and temporal area in young infants. This seems to be because of region-dependent brain maturation. Myelination overall progresses slowly in most of the occipital area (Flechsig, 1901), in contrast to the sensorimotor area and the temporal area. Recent infant NIRS studies are consistent with this neurophysiological development, and neonates typically show normal HRF for temporal areas in response to speech (e.g., Gervain, Macagno, Cogoi, Peña, & Mehler, 2008; Peña et al., 2003). In the case of premature infants, our recent data with speech stimuli (Arimitsu et al., 2018) revealed an inverted HRF in many preterm infants. Further examination showed that HRF typicality is not significantly correlated with the duration of language exposure (i.e., age after birth), but with corrected gestational age (i.e., maturational age), suggesting that more typical forms of brain responses to speech parallel neurophysiological development.

Apart from physiological maturation, such HRF variation in response has been attributed to differences in attention and the level of consciousness (Taga, Asakawa, Maki, Konishi, & Koizumi, 2003). Inverted HRFs do not always mean "deactivations," despite a functionally related decrease being the dominant explanation for an inverted HRF. In fact, data gathered in our lab from full-term neonates revealed an inverted HRF response to mother's speech as opposed to a normal HRF response to non-mother's speech (Uchida-Ota et al., 2014). This difference cannot be explained by immature brain development because these neonates showed normal patterns to a non-mother's voice stimuli in the same experiment; additionally, behavioral studies have revealed a special role of mother's speech even in fetuses (e.g., Kisilevsky et al., 2003). As the decrease was observed strongly in the dorsomedial prefrontal area, external attention to the stimuli is one of the explanations (Gusnard & Raichle, 2001). As similar task-induced decreases in brain activity have been frequently discussed in fMRI literature (e.g., Binder, 2012), readers will find more detailed descriptions there. Although both physiological and functional mechanisms of HRF patterns are yet to be fully understood, NIRS's sensitivity to oxy- and deoxy-Hb will further clarify interpretations of hemodynamic signals in NIRS, positron emission tomography (PET), and fMRI experiments.

Temporal and Spatial Resolutions

The temporal resolution of fast NIRS is 10–100 Hz and that of CW NIRS is around 5–10 Hz (Figure 7.4). However, because of the slow hemodynamic response to neural activation, temporal activation is effectively around 0.3–0.5 Hz. The temporal resolution of CW NIRS is comparable or better than fMRI and PET, but inferior to MEG (see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume) and EEG. Thus, it is difficult to obtain a detailed time course of each cognitive stage in language processing. In general, brain activations during cognitive tasks within a block lasting 10–30 s or an event lasting 3–5 s are examined (see later discussion in this chapter for more detail). Yet if two distinctive cognitive processes (e.g., encoding and retrieving) are well separated in an experimental task, NIRS can capture each response in a form of two peaks within one curve (Miyata, Watanabe, & Minagawa-Kawai, 2011). Furthermore, peak latency can serve as a good parameter to examine the effectiveness of language processing. A NIRS study that investigated 4-month-old infants listening to various auditory stimuli (Minagawa-Kawai et al., 2008) indicated about a 2-s delay in peak latency for the hemodynamic response in the auditory area compared to the canonical HRF. Another example involves learning of phonemic contrasts that frequently and infrequently occur within one language (Tsuji et al., 2017). In 5- to 8-month-old Dutch infants, a frequent contrast evoked earlier response peaks than an infrequent one, suggesting a neural efficiency attuned by the frequent phonemic exposure.

Spatial resolution can be characterized as lateral (parallel to the brain surface) or depth resolution, both strongly dependent on the arrangement of source and detector fibers on the scalp. Indeed, one can improve lateral resolution by increasing density

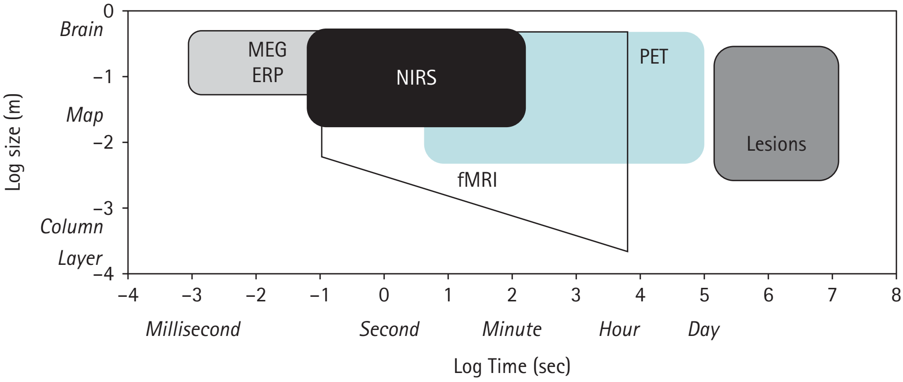

FIGURE 7.4. Spatial and temporal resolution of a variety of techniques for the study of brain function.

(bearing in mind limitations related to light traveling in tissue; Yamamoto et al., 2002), and depth resolution by using multiple source-detector separations. In adults, diffuse light reflection between white and gray matter limits depth resolution even if source-detector distance is increased, whereas information from deeper regions can be obtained in neonates due to the lower density of white matter (Fukui, Ajichi, & Okada, 2003). Overall, the spatial resolution of CW NIRS is superior to EEG and MEG but inferior to fMRI at the cortical surface. Unlike fMRI, fNIRS experiments usually measure targeted brain areas by attaching some probe pads onto regions of interest. We will mention how to place the pads to examine language-related areas later in this chapter.

Comparison with Other Methods: Pros and Cons

Advantages

One of the strong advantages of NIRS is its flexibility and innocuousness. In addition to the fact that multi-channel NIRS systems are portable, NIRS with flexible optical fibers can accommodate almost any head position and posture, and can tolerate a degree of head movement. These advantages allow its use in various types of experimental settings and tasks, including interpersonal communication and language-production tasks. Above all, these advantages enable examination of young infants, children with developmental disabilities, and people of all ages with cochlear implants. In contrast, fMRI requires the infant's head to be held stationary for long periods so that infants have to be asleep (naturally or sedated). Consequently, fMRI is not normally the primary choice for studies on the developing brain, although infant fMRI studies, particularly studies on anatomical structures and resting state, are rapidly multiplying.

Another advantage of fNIRS over fMRI related to the study of language is that optical techniques can be conducted in silence, whereas an MRI scanner is a very noisy environment. Some additional advantages of NIRS over fMRI include its lower cost and compatibility with other electrical or magnetic monitoring systems (e.g., eye-tracking system, electrocardiograph, and EEG) and therapeutic devices.

Although EEG shares some of the same advantages as NIRS methods compared to fMRI, such as portability, silent operation, and tolerance of posture, its ability to localize the focus of activity is generally poorer than that of fNIRS. Because the electrophysiological signal is so weak, many repetitions of stimulus events are required to be able to average out noise, which results in a longer experimental session with EEG than with fNIRS. In addition, most EEG systems require more careful electrode placement than fNIRS, which takes a relatively long time. MEG is far superior to EEG in these respects. However, MEG requires a strict fixation of the participant's head relative to the sensor assembly, which often requires sedation for young participants. Both EEG and MEG are excellent at resolving millisecond neural events, which escape fNIRS.

Limitations

While fNIRS represents a potentially powerful tool for cognitive studies, it has several crucial limitations. NIRS offers poorer spatial resolution and depth sensitivity than fMRI, which prevents us from measuring deep regions such as the basal ganglia in relation to language/grammar, or the amygdala and hippocampus in relation to emotion and memory processing. However, many other language-related areas, namely superior temporal gyrus (STG), supramarginal gyrus (SMG), angular gyrus, and inferior frontal gyrus (IFG), can be recorded.

Another difficult issue is that NIRS signals measured from the scalp surface include systemic vascular effects not only from inside, but also from outside the brain. These changes originate from cardiac and respiratory pulsations, physiological vasomotion (Mayhew et al., 1999), and low-frequency oscillations (Katura, Tanaka, Obata, Sato, & Maki, 2006). Therefore, it is important to use experimental tasks that do not evoke large systemic vascular changes, unless they are independently monitored (e.g., heart rate, blood pressure, and skin conductance). This may not be a big issue in typical language tasks, where no strong emotional factors are evolved.

Another potential problem is the change in blood volume in the scalp and within the muscles beneath the optical probes. There are some crucial points to consider in designing experimental tasks with NIRS. Although a language-production task or oral response to a question is feasible with fNIRS, one must first make sure that the probes do not sample from tissue where blood flows toward the specific muscles, including the so-called temporal muscle. Similarly, when performing studies of interpersonal communication, one must be careful that signals picked up on probes placed on the forehead are not contaminated by local movement due to the participant producing facial expressions involving this area. Head position may also affect blood volume. For instance, if a participant tilts his or her neck to the right, the blood volume will increase on the right side, resulting in Hb signal changes. Such false-positive brain activation caused by neck tilting has been examined in relation to the area volume of the common carotid artery and internal jugular vein (Takeda, Gunji, Watanabe, & Kato, 2008).

A standard method to exclude systemic vascular effects from external or noise signals is lacking for NIRS, but a variety of methods have been investigated in this respect (see discussion of data analysis later in this chapter). Further clarification of the systemic vascular changes and hemodynamic physiology of the brain are necessary to establish a standard framework for data analysis. Discussions of further technological or methodological issues related to NIRS can be found elsewhere (Aslin & Mehler, 2005; Hebden, 2003).

EXPERIMENTAL DESIGN AND ANALYSIS

Designing an optimal experimental paradigm is crucial to perform a successful NIRS experiment, just as in other neurocognitive techniques. Because experimental design is critically related to the analysis methods that can be applied, this section describes some key aspects of the analysis methods, and provides readers with elementary knowledge concerning study design, including task selection and experimental time intervals. Experimental design and analysis methods of NIRS are roughly comparable to those for fMRI because both methods are based on hemodynamic parameters. Thus, analysis methods for NIRS can utilize standard methods in fMRI, such as general linear models (GLM) and connectivity analyses. However, the fact that measurements are derived from sensors placed on the scalp leads to other aspects being more similar to analyses for EEG, as exemplified by the questions regarding sensor attachment.

How to Schedule Time Intervals

Block Design

As in BOLD fMRI, the block paradigm and the event-related (trial-based) paradigm are the two major designs used to measure the hemodynamic responses in fNIRS studies. In the block design, individual stimulus trials or events are tightly clustered into "on" periods of activation, alternated with "off" control periods (e.g., alternating 20 s "off/rest" and "on/task" periods). Because this method generally employs long "on" periods ranging from 10 to 40 s, relatively large brain activations are usually obtained. Therefore, a large number of blocks (a set of "on" and "off") repetitions is not usually necessary, and one can perform several conditions for "on" periods within one session. In our studies (Minagawa-Kawai, Mori, Sato, & Koizumi, 2004; Arimitsu et al., 2011), for example, a phonemic condition and a prosodic condition are pseudo-randomly presented as "on" periods against a control condition as "off" period within a single session. This kind of block design has been widely used in language studies with NIRS for both children and adults. To determine the language laterality for patients requiring surgery for seizure relief, a word fluency test is employed with NIRS (Watanabe et al., 1998). Patients are instructed to write words starting with a certain letter of the alphabet presented for each "on" period, while during the "off" period they draw a picture by copying a prepared stimulus as a control task.

Event-Related Design

Neural activity in response to specific events can be time-locked using an event-related design (Friston et al., 1998; Friston, Zarahn, Josephs, Henson, & Dale, 1999; Zarahn, Aguirre, & D'Esposito, 1997). Hemodynamic changes can be measured in response to single events, such as performing one trial or the onset of a single movement. After the single event, a baseline period which usually has various time intervals are inserted. In general, Hb changes to any one trial are too small to detect; accordingly, averaging numerous trials is necessary to obtain a clear signal. Nevertheless, there are various advantages favoring an event-related paradigm over a block design. For example, while participants can sometimes anticipate the next stimuli in a block design, the event-related design keeps the participant's attention uniform without anticipation. Furthermore, the random time intervals prevent Hb data from being contaminated by systemic vascular signals such as heart beats. Variable time intervals increase statistical power (Birn, Cox, & Bandettini, 2002). The event-related design significantly broadens the types of neural processes that can be investigated.

HRF and Time Schedule

Performing pilot studies to fix the experimental time schedule is important, because the optimal time schedule must provide a large enough HRF in response to the stimuli/task, and such optimal timing varies depending on the stimuli/task. In a study on phonological grammar, Minagawa-Kawai et al. (2013) showed that a certain combination of experimental conditions worked better, and led to obtaining an HRF that was more than five times larger than other conditions. Specifically, a longer stimulus period with more salient auditory stimuli evoked larger responses than "on" blocks that were shorter and with more similar stimuli. Another issue of interest pertains to the length of the rest period. Ideally, one must have a good idea of the expected time course of the hemodynamic response elicited by an intended task, so as to set up a long enough rest period. Neural activation causes changes in Hb, an increase in blood flow, and increases in local oxygenation (Fox & Raichle, 1986). Typically, hemodynamic responses should return to baseline during the rest period to facilitate the separation of Hb signals between the task and rest periods. As shown in the fMRI literature, the time latency and amplitude of hemodynamic responses vary depending on the region and the task. Thus, the timing of Hb return should be checked in a pilot study. We note that this is particularly desirable when doing averaging analyses, but it is not relevant when applying GLM analysis, because one can use a de-convolution process with GLM. If we assume that the cerebral responses to different and successive cognitive events are linearly accumulated, then each response curve can be separated by the de-convolution procedure, provided different conditions are presented (Wobst, Wenzel, Kohl, Obrig, & Villringer, 2001).

WHERE TO ATTACH THE NIRS PROBE

According to the study hypothesis, one should first decide the regions of interest, which should be on the cortical surface. Usually, the NIRS probe pad is attached such that the most focused area can be precisely covered by some pairs of emitter and detector. In targeting the STG as posterior language area, for example, T3 and T4 positions (from the international 10–20 system) are typically used as landmarks in attaching the probes

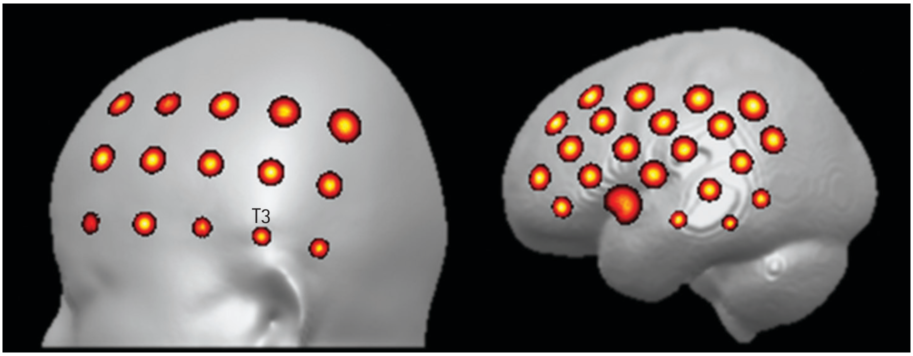

FIGURE 7.5. An example of probe attachment to measure language areas. 3 x 5 optode array was fitted to temporal and frontal areas using landmarks of the international 10–20 method (left). Estimation of brain regions and channel positions (right).

by employing a procedure called *spatial registration* (Tsuzuki et al., 2007). In the case of a 3 x 5 optode (optical sensor) array, if we place one probe onto T3 and position the bottom probe line to be roughly fitted on T3-Fp1 line (Figure 7.5 left), channels positions are estimated to cover left temporal brain regions as indicated in Figure 7.5 (right). This positioning allows us to measure the SMG and IFG and is thus suited to examine the language network in the perisylvian area. This registration method has been developed to probabilistically register NIRS data onto the Montreal Neurological Institute (MNI) coordinate space or Tarailach coordinates without using anatomical MR images (Okamoto et al., 2004; Tsuzuki et al., 2007). Although this method is currently generally applicable to adult brains, it can be applied to infants and children under some conditions of probe alignment. As for school-age children, this method is applicable without any additional procedures because brain sizes are almost identical between school-age children and adults (Sugiura et al., 2011). Spatial registration methods are still in development, and various new methods have been proposed (Tsuzuki & Dan, 2014). (Spatial estimations of various probe arrays are available at http://brain.job.affrc.go.jp/resources/index.php.) Therefore, one way to decide the attachment location is to refer to these estimation results. However, in employing this method, it is necessary to precisely measure head sizes, following the international EEG 10–20 system.

LANGUAGE TASKS

Almost all language tasks performed in fMRI studies are applicable to fNIRS. Several other tasks are additionally possible with fNIRS because of its tolerance for participant motion. Participants are able to conduct movement tasks, as exemplified by a series of fNIRS studies on motor skills and rehabilitation (Hatakenaka, Miyai, Mihara, Sakoda, & Kubota, 2007; Miyai et al., 2001; Miyai et al., 2003.). Thus, writing, reading, speaking, and listening tasks are all appropriate. If adequate space and channels are available, it is feasible to simultaneously measure and examine the interactive communicative processes of two people. Wireless NIRS will further expand its task applicability. Nonetheless, some considerations unique to fNIRS should be taken into account when designing tasks. First, it is necessary to preclude tasks that trigger large facial movements or other specific motion-related artifacts. As stated previously, the experimenter should carefully check for movement in the temporal muscle when employing an oral pronunciation task. Emotional stimuli affect the facial expressions of participants, causing artifacts in the probes placed on the forehead. Emotional stimuli also affect the systemic vascular change, which in turn influences NIRS signals. It is therefore recommended that biological signals such as blood pressure and skin circulation be monitored while performing emotional studies (see discussion of co-registration later in this chapter).

In performing an fNIRS experiment, additional behavioral testing prior to or after the fNIRS testing is sometimes very useful for interpreting fNIRS data. In a study where we examined infants' brain responses to their own and other names (Imafuku, Hakuno, Uchida-Ota, Yamamoto, & Minagawa, 2014), behavioral attention while hearing the names measured in a separate behavioral test correlated well with the amplitude of brain responses from dorsomedial prefrontal cortex, suggesting a functional role for that region. Apart from the task, other general assessments, including handedness, development, and intelligence, are also useful indices to verify participants' general cognitive abilities.

COMBINING NIRS WITH OTHER MODALITIES

NIRS can be easily combined with other physiological measurements. To compensate for the low temporal resolution of NIRS, combining it with EEG or MEG is advised (e.g., Telkemeyer et al., 2009). Since NIRS data are affected by systemic vascular signals, measuring such external signals outside the brain (e.g., blood pressure and respiration) is also useful (Katura et al., 2006). Because mothers' infant-directed speech increases or decreases infants' heart rate (DeCasper & Fifer, 1980), it is possible that such a vascular change affects NIRS signals. By taking this issue into account, we are currently performing a study of NIRS in combination with EEG, electrocardiograph, and respiratory measurements. This type of experiment can provide insights into a possible relationship between brain function and the autonomic nervous system. As is frequently employed in fMRI experiments, recording eye movements at the same time as the NIRS measurement is also useful to interpret the Hb data. By combining NIRS with eye-tracking measurements on fast-reading specialists and normal readers, Miyata et al. (2011) found that cerebral activity around the angular gyrus was related to reading speed. If metal free NIRS is available, fMRI-NIRS is feasible. This combination would be beneficial to study the physiological bases of BOLD fMRI because absence of a BOLD response does not always mean an absence of brain activation, as revealed by NIRS measurements (Seiyama et al., 2004).

DATA ANALYSIS

NIRS lacks a standard method or software for data analysis, unlike fMRI studies, which have some powerful parametric mapping tools such as SPM (see Heim & Specht, Chapter 4 in this volume). However, there are some basic processes for data analysis that have been employed in many NIRS studies. Here, we provide a quick summary of such fundamentals of NIRS signal processing. As we have already described how attenuation (absorbance) data are converted to Hb data, we will start with the preprocessing of Hb data, which usually consists of artifact rejection, filtering, and detrending (Figure 7.6). Then several methods to evaluate the data, including averaging and GLM, are illustrated, followed by information about analysis software that is available for free.

Artifact Rejection

NIRS data contain a variety of irregular signals, primarily due to body movement and loose probe attachment. Artifacted blocks and/or channels are usually removed as a whole, but depending on the case, artifacted data can be dealt with using certain mathematical methods (e.g., linearly interpolating a short missing stretch, or in GLM giving that region of the signal a weight of zero in the regression). Although artifacts are characterized by a sharp change that can be detected easily by the human eye, objective methods such as setting a threshold using the standard deviation of the Hb data are

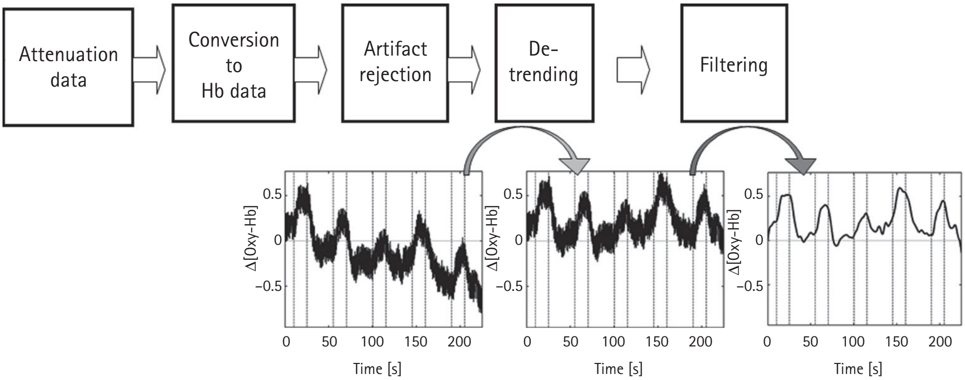

FIGURE 7.6. Several stages of pre-processing the NIRS data.

Source: Three figures at the bottom are taken from Takeda (2007).

generally employed. Several additional methods are employed to exclude external noise, such as wavelet-based algorithms (Sato et al., 2006) and principal component analysis (Zhang, Brooks, Franceschini, & Boas, 2005).

Filtering

NIRS data contain vascular signals due to cardiac and respiratory pulsations and physiological vasomotion (Mayhew et al., 1999). Raw data consist of various frequency components, some of which may be noise. The activation signals must be reliably separated from those of the noise components. Filtering removes this type of baseline frequency. The choice of filter types (high-pass, low-pass, band-pass, or band-elimination) depends on the type of noise component to be excluded. A moving average is another method to smooth data. A wide range of high-frequency components can be eliminated with a longer duration moving average. This means that the moving average functions as a low-pass filter.

De-trending

Concentration changes measured with NIRS tend to show constant increments or decrements, mainly due to natural physiological fluctuations (Figure 7.6). The de-trending process works to remove such linear drift. With a GLM approach, which will be mentioned in the last part of this section, the filtering and de-trending processes can be achieved by employing multiple regressors in the design matrix.

Hb Parameters

NIRS studies generally employ oxy-Hb as the dependent measure when examining brain activation. Although it is generally accepted that oxy-Hb and total-Hb are correlated with BOLD (Strangman et al., 2002), the relationships between Hb parameters and BOLD obtained in prior studies are sometimes conflicting (Steinbrink et al., 2006). Huppert, Hoge, Diamond, Franceschini, and Boas (2006), for example, reported that oxy-Hb has a higher SNR, whereas deoxy-Hb better reflects region-specific activation.

Averaging Method

Averaging is widely and routinely used to analyze EEG data. Typically, after integrating information across all the blocks to derive a grand-averaged Hb time-course (Figure 7.7, top right panel), oxy-Hb changes during the baseline period and the task (stimulation)

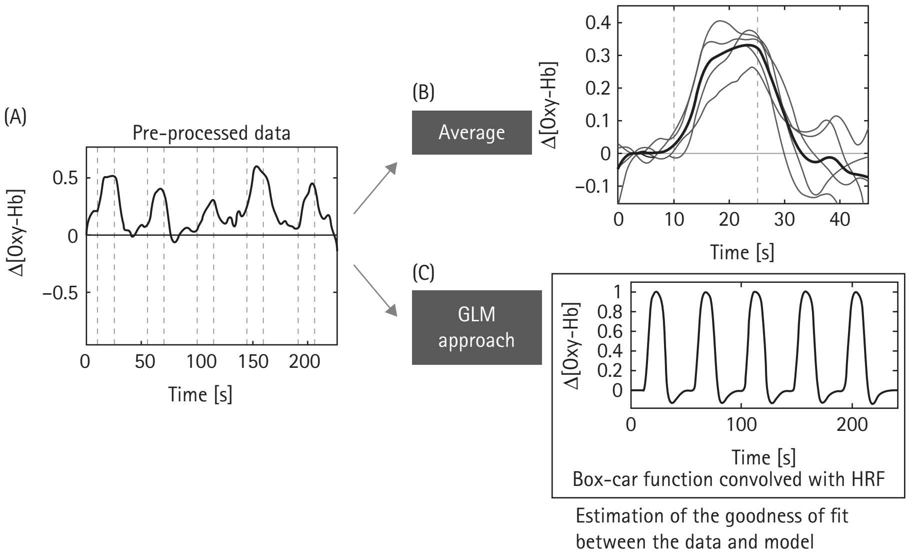

FIGURE 7.7. Analyzing pre-processed data (A) with averaging (B) and GLM (C) methods.

Source: These are modified figures, each of which is taken from Takeda (2007).

period are compared. As the number of blocks increases, random background noise diminishes, and more function-related brain signals can be extracted. Similar to EEG, time windows for baseline and task periods are set, and the averaged values for each participant are subjected to a second-order analysis with a *t*-test or an analysis of variance (ANOVA).

General Linear Model (GLM)

The GLM approach is typically employed in the analysis of BOLD-fMRI data (e.g., Friston, 1994). Although this approach is very popular in the field of fMRI, it is employed more rarely in NIRS. In plain terms, GLM estimates the association between brain-scanner data and an ideal brain-activation model, which is a linear combination of a set of modeled HRFs plus random noise. If the response data fit well with the model response, which indicates a high correlation, then one can say that the data show strong brain activation. Pre-processed raw data (Figure 7.7, left panel), for instance, can be evaluated with the model indicated in Figure 7.7 C (bottom right panel). This model is simple in that it only contains a prediction of the expected HRF response, but other variables can be added to the analysis matrix so as to model certain aspects of the "noise" (e.g., sine and cosine functions at different periods to filter out vascular signals). It is difficult to identify an optimal analysis matrix a priori (i.e., how many and which type of models to include to best represent the study outcomes). Using more model functions than necessary lowers the sensitivity by taking up degrees of freedom, whereas an insufficient model may enhance the risk for systematic errors, resulting in lower statistical power. Although selecting the optimal model is critical, it may vary depending on the brain region of interest, experimental time setting and task, and age of the participants (e.g., adults vs. infants).

Connectivity Analysis

Functional connectivity has been increasingly popular in fMRI studies in the last decade, and fNIRS has also employed some techniques borrowed from fMRI, as exemplified in the following review section. Due to differences in measurement principles and limited measurement of brain areas in NIRS, not all the methods from fMRI can be used for fNIRS analysis. At present, cross-correlation and phase-locking analyses are some representative methods to assess connectivity. To assess the connectivity between two persons, namely, synchronicity of the brain activities in two persons, wavelet coherence is typically used.

Available Software for NIRS Analysis

A variety of software for fNIRS analysis is available. These include HomER, functional optical signal analysis (foSA) (Koh et al., 2007), NIRS-SPM (Ye, Tak, Jang, Jung, & Jang, 2009), and Platform of Optical Topography Analytic Tool (POTATo) offered by Hitachi. Most are custom Matlab programs, which are available as freeware. A package for spatial estimation is available at http://brain.job.affrc.go.jp/resources/index.php.

Language Studies with fNIRS: A Brief Review

In this section, we review a handful of NIRS studies bearing on language acquisition. Our goal is not to provide an exhaustive review, but rather to introduce a few examples illustrating the strengths and limitations of the technique for the study of language acquisition. Readers interested in more extensive discussions can read Quaresima, Bisconti, and Ferrari, (2012) for an overview of fNIRS studies on language processing across the life span; and Aslin (2012) for a recent summary and critique of infant fNIRS studies, including language. Here, we will cover only three salient topics: the biases leading to left dominance; the development of brain networks engaged during language processing; and some clinical applications. Our closing words highlight the unique advantages of fNIRS research for the study of language acquisition.

Biases Leading to Left Dominance

It is clear that linguistic knowledge and neural implementation go hand in hand, such that localized damage to the brain results in specific linguistic impairments. Moreover, differences in speech perception due to diverse linguistic experiences are expressed through differences in neural commitment (e.g., Lenneberg, 1966). This work has highlighted the engagement of perisylvian cortices in the left hemisphere for speech processing (e.g., Binder et al., 2000; Zatorre & Gandour, 2008). But what are the biases driving this left-lateralization in the engagement of cortices in the STG and superior temporal sulcus (STS)? Previous work, primarily with adults, has suggested that speech may be associated with left dominance due to (a) its acoustic characteristics; and/or (b) its intrinsic linguistic nature. Signal-driven hypotheses propose that the rapid, changing acoustic nature of spoken stimuli is better captured by the left hemisphere neural structures (e.g., Zatorre & Belin, 2001), while domain-driven theories argue for an innate language module located in the left perisylvian area, which detects and processes language already at birth (Dehaene-Lambertz & Gliga, 2004).

Adult evidence is equivocal on the question of what shapes such language networks, since all the many factors that could be playing a role (e.g., acoustic and language experience) are confounded. Moreover, although it is possible to test infants with EEG, MEG, and fMRI, the first is not ideally suited to answer questions of strict localization, and the latter two are both challenging to implement for infants and relatively expensive. In this context, cheap, infant-friendly NIRS has provided the field with a much-needed tool to investigate the differential engagement of left and right perisylvian cortices in two ways. First, it has allowed researchers to measure the effects of the careful manipulation of specific factors, associated with the two families of hypotheses noted earlier (signal- and domain-driven), in healthy newborn infants, a population that is challenging to neuroimage otherwise. The ease with which newborn fNIRS studies are carried out effectively means that many more research groups can gather independent, complementary evidence on the same question. Second, NIRS also facilitates tracking developmental curves because the technique is applicable to a range of ages, including awake mobile toddlers. As we will see, both of these features have been critical to shedding light on the ontogenetic origins of left-dominant language processing.

We begin with a specific example. Telkemeyer et al. (2009) investigated a specific hypothesis within the signal-driven class, according to which left auditory cortices respond more than the right when presented with short sounds, whereas the opposite lateralization should be observed for longer sounds. When newborns were presented with these two types of auditory stimulation, one channel tapping temporo-parietal cortices showed the predicted crossover, although this asymmetry was not strong enough to survive correction for multiple comparisons. Using a different set of stimuli that manipulated spectral entropy (fast versus slow changes), Minagawa-Kawai, Cristia, Vendelin, Cabrol, and Dupoux (2011) also failed to uncover any modulation of the *asymmetry* of the activation (although they found a modulation of the *size* of the activation). Together, these studies suggest that these two specific instantiations of the signal-driven hypothesis might not apply to the newborn brain, and that others should be entertained (although see Poeppel, Idsardi, & van Wassenhove, 2008, for an argument that signal factors explain right-hemispheric engagement rather than left-dominance per se).

As mentioned earlier, signal-driven hypotheses are one of the two mainstream families of explanations attempting to account for left-dominant cortical engagement during language processing. The second family proposes that in addition to, or instead of, any signal-driven biases, left perisylvian cortices are innately prepared to process linguistic material. We have reviewed infant neuroimaging evidence from birth through adulthood by evaluating results against the predictions made by each family of explanation (Minagawa-Kawai et al., 2011). We concluded that neither the signal-driven nor the domain-driven explanations, on their own, sufficed to cover extant findings. Instead, we proposed that these two and a third explanation must be weaved together, as follows. Early on, slow and/or prosodically rich stimuli modulate right-hemispheric STG and STS engagement, whereas to a certain extent left-dominant activations must await infants' retrieval of certain abstract properties in their input, such that the domain-driven biases are established at least partially via learning.

Evidence corroborating this proposal comes from three newborn NIRS studies. Peña et al. (2003) presented Italian newborns with infant-directed sentences in Italian played forward or backward, and found that the strongest discrimination between these two types was found in left channels tapping STG and/or STS. Two groups carried out independent extensions of that work, crossing the direction factor (forward versus backward) with a familiarity factor (native versus foreign speech). Sato et al. (2012) presented Japanese newborns with infant-directed Japanese and English, both forward and backward, and they replicated Peña's findings in the Japanese forward-backward comparison, but not with the English stimuli. For their part, May, Byers-Heinlein, Gervain, and Werker (2011) tested Canadian-English neonates with English and Tagalog forward and backward sentences that had been low-pass filtered, such that the intonation and rhythm were perceptible, but their segmental properties were otherwise removed. No asymmetry in processing was apparent in the latter study. Taking all three studies together, we can see that the activation of left STG/STS is *not* modulated by direction when only the slow, prosodically rich components of speech are presented. In contrast, when speech is presented in all its complexity, left-dominance occurs for *familiar* forward stimuli, fitting with the notion that domain-driven biases benefit from learning. In the present case, learning will have occurred in the womb, as much previous behavioral evidence has shown tuning to the native language's broad characteristics by birth (e.g., Mehler et al., 1988).

As mentioned earlier, NIRS also provides a window on development by virtue of being applicable to a range of ages. The prime example comes from studies on processing of sound contrasts. In our review (Minagawa-Kawai et al., 2011), we identified nine such experiments on infants 0–20 months of age and adults, covering the full range of contrasts employed in the world's languages (consonants, vowels, duration, and tones) in addition to non-segmental contrasts (prosody). Some of the contrasts were present in the listener's native language, and others were not. In general terms, one observes that discrimination of sound contrasts, regardless of the type and the native status, are processed bilaterally early on, with increasing lateralization (left-dominant for native contrasts, right-dominant for prosodic contrasts) with age, which is already clear at 10–20 months. We will return to this age range later, but for now we note that this evidence fits well with the proposal of lateralization for linguistic processing being reinforced as a function of both age and experience.

In sum, this section has summarized a few fNIRS studies bearing on the very early sources of leftward asymmetries in STS/STG during language processing. We have seen that this research profits from the technique of NIRS through independent conceptual replications as well as longitudinal comparisons, which together suggest that there is a developmental and experiential component to asymmetric language processing.

The Development of Brain Networks

The previous subsection dealt with a question for which NIRS was useful because of the possibility of assessing asymmetries in localized activation. In the present subsection, we deal with another problem related to localization, namely the emergence of larger networks, involving multiple cortical regions. Indeed, it is widely agreed upon that to explain language processing we must not only describe localized activations, but also how activation is correlated across different regions. There are only a handful of studies assessing global networks with EEG and fMRI in infancy and childhood (see Chu-Shore, Kramer, Bianchi, Caviness, & Cash, 2011, for a review), and none of them bears directly on language acquisition.

This is, for the time being, a question on which there is evidence from only one lab (as of 2014). Using a unique high-density NIRS system, Homae, Taga, Watanabe, and colleagues have investigated correlations in low-frequency oscillations across 94 measurement channels, distributed around the head to tap frontal, temporal, parietal, and occipital regions.

In one study (Homae, Watanabe, Nakano, & Taga, 2011), this pad was used to collect data from 3-month-olds during three 3-minute periods: quiet, awake resting state; stimulation with recorded spoken passages; and another silent period. The correlations found during the initial resting state replicate those found in a previous study (Homae et al., 2010): They were stronger within regions and within hemispheres than between regions or hemispheres. During speech stimulation, this pattern changed somewhat, with strengthening of fronto-temporal correlations, particularly in the left hemisphere. This altered pattern was maintained during the third, quiet, period, suggesting that strengthening of fronto-temporal correlations was not solely due to the direct effect of speech stimulation, but indicated instead the involvement of an emergent functional network.

Interestingly, the same effects were observed when the stimulation consisted of pure tones (Taga, Watanabe, & Homae, 2011), suggesting that this precise functional network may not be specific to language processing. Our data (Uchida-Ota et al., 2014) add some insights into this. We measured 37 full-term neonates to examine connectivity during listening to infant-directed speech, spoken by either their mother or a stranger, using phase-locking analysis. Mother's speech exclusively evoked a strong and dense fronto-temporal connectivity. Connectivity between STG and inferior frontal areas was specific to mother's speech. We would look forward to additional studies that may shed light on networks that are specifically involved in linguistic processing, either by testing older infants and children (who would presumably be proficient enough to carry out such operations) and/or by using stimulation paradigms that help infants focus on linguistic aspects of speech, rather than solely the acoustic ones.

Some Clinical Applications

The prime example of clinical application of NIRS comes from the study of language processing by individuals with cochlear implants. Since the implant is typically an electrical device with metal parts, it is not possible to use MRI with implanted individuals, and the EEG/MEG signal has to be carefully sifted due to the interferences from the device itself (when it is turned on). Thus, fNIRS research is in a unique position to shed light on language processing by infants and children who have received cochlear implants.

We report on an example of this literature in some detail both because it illustrates this unique vantage point, and because it allows us to bring out some strengths and weaknesses of the application of NIRS to study language acquisition among clinical populations. Sevy et al. (2010) measured responses to speech in left and right temporal cortices in four populations: a group of normal-hearing adults; another of normal-hearing children (aged 4–15 years; 9 years old on average); a group composed of deaf children with at least 4 months of use of a cochlear implant (aged 2–19 years; 8 on average); and a group of deaf children at the moment of activation of the cochlear implant (aged 2–8 years; 5 on average). Several aspects of their data are of keen interest to us, as follows.

The first relates to the proportion of participants whose data could be included because they accepted the cap and were quiet enough during testing. This percentage was 92% among normal-hearing children, 93% among experienced cochlear-implant children, and nearly 70% among the younger children whose implants had just been turned on. These acceptance rates are encouraging because they suggest that NIRS may be a technique that could be used with a majority of participants.

Second, and also on the methodological side, they found significant activations to speech (in oxyHb and/or deoxyHb) for 100% of adults; 82% of normal-hearing children; 76% of experienced cochlear users; and 78% of the children tested at activation. Notice that percentages are very similar across all child groups, and differences across the groups do not correlate with differences in perceptibility that are likely found between (inexperienced) cochlear users and normally hearing children. The fact that percentages are lower among all child groups than the adults suggests a limitation of the technique, since they were all stimulated with the same sounds but activations were not registered in all cases. What may be the reasons for such variability? We know that children have thinner skulls, such that their optical data are both stronger and less affected by surface artifacts than adults. Thus, weaker sensitivity is not a convincing explanation. In contrast, three explanations related to weaker signals seem more convincing. It is possible that children payed less attention to the stimuli, and narrower cortical regions were therefore activated (potentially limited to primary auditory areas, which, located in sulci, are less accessible with NIRS). Furthermore, individual differences in functional engagement of a given cortical region might be greater among children than among adults. Finally, there may be more variability in scalp-to-cortex mapping among children than adults, leading to greater cap placement errors (even when surface landmarks are carefully used) in the former than the latter population.

Regardless of these limitations, a further aspect of their data illustrates the potential of such studies to inform psycholinguistic research. We have explained earlier the interest in studying lateralization for speech processing. We might then wonder, comparing the three groups of children, whether lateralization patterns may differ among the groups, given that two of them have lacked exposure to speech during the critical period of infancy. In fact, responses in the two clinical groups were stronger and more stable (at least in terms of oxyHb) in the *right* than the left hemisphere, whereas the normally hearing children exhibited a clear left-dominant response. One aspect of these results is, however, intriguing: Adults, like the two clinical groups, showed clearer responses in the channels located on the *right* hemisphere. Given the stimuli samples were not chosen to isolate specific characteristics (e.g., processing of segmental contrasts), we cannot easily explain either the right bias observed in adults, or the observed differences among the child populations. More research is needed to understand whether these diverse lateralization patterns were specific to speech (by comparison to, e.g., music), and to what extent they were affected by age and amount of auditory experience.

Before closing this section, we mention two additional strands of literature illustrating clinical applications of NIRS. By virtue of its ease of use, innocuousness, and portability, NIRS is a good tool for bedside testing of a number of clinical populations. Many studies have been carried out on preterm infants and infants that are hospitalized (due to low birth weight, respiratory distress syndrome, etc.). A number of these studies are closely related to the hospitalization experience (e.g., response to pain; Slater, Cantarella, Franck, Meek, & Fitzgerald, 2008) or on the correlates of simple perception (odor, auditory, visual, etc.; e.g., Kusaka et al., 2004). An interest in language is rarer, and the evidence is too scarce, at present, to reveal patterns that are of specific interest to psycholinguists. For example, Nishida et al. (2008) report that temporoparietal channels respond to speech faster in infants born preterm tested around their due date compared to full-term neonates tested shortly after birth. It is unlikely, however, that this reflects differential *linguistic* processing of the speech signal, since a similar pattern (faster responses in preterms than full-terms, matched in gestational age) had been found with sinewave tones (Kotilahti et al., 2005). Moreover, one cannot, at present, be certain whether such differences in processing should be attributed to the infants' differential life experience and/or differences in neurological development caused by their perinatal conditions (see Bosch, 2011, for a recent discussion of literature on preterm speech processing and language acquisition).

Additionally, NIRS can also be used with any other clinical population. For instance, a recent strand of work focuses on lateralization patterns in children with a diagnosis of autistic spectrum disorder (ASD) (Minagawa-Kawai et al., 2009), and in children who stutter (Sato et al., 2011). Minagawa-Kawai et al. (2009), for instance, presented ASD children (aged 9 years) and typically developing children (aged 7 years) with blocks of words such that, within a block, the same word was repeated over and over (e.g., itta itta itta . . . ; these are called *non-alternating blocks*) or alternated with a minimal pair (e.g., itta itte itta . . . ; these are called *alternating blocks*). Previous work had shown that, when presented with an alternation of vowels, as in the example just given, adults and normally-developing toddlers show left-dominant responses in STS/STG (Furuya & Mori, 2003; Sato et al., 2003). Minagawa and colleagues replicated these results in their sample of normally developing children, whereas responses in a group of autistic individuals were perfectly bilateral.

Final Remarks

Before moving on, we would like to point out some populations and topics in which NIRS does not hold a particular advantage. In this section, we have focused more on infants than young children, and very little on older children, in part because this reflects the amount of research that is done on each age. It is widely believed that the early years make a greater contribution to first language acquisition than later ones (e.g., Dupoux, Peperkamp, & Sebastian-Galles, 2010), which may in part explain the bimodal distribution of ages tested. Nonetheless, children of some ages (saliently between 1.5 and 2.5 years of age) are simply more difficult to test, and NIRS caps, albeit generally well accepted (as we saw in the numbers from Sevy et al., 2010), still need to be placed and tolerated for long periods of time.

We have not reviewed research on second-language acquisition, despite the fact that it is a topic that has attracted some attention in the NIRS literature (Minagawa-Kawai et al., 2004). This is simply because NIRS advantages and disadvantages for this topic are roughly the same as those we have mentioned elsewhere—there may be more labs using it because it is inexpensive, but nothing specifically recommends NIRS for the study of this topic.

FUTURE PROSPECTS

NIRS has a huge potential for various applications in relation to language because of its innocuousness and mobility. Applications for brain-machine interfaces is one example, as NIRS could conceivably be used to pick up brain signals and convert them into speech production commands for patients of amyotrophic lateral sclerosis or patients without vocal tract. In fact, a very primitive level of such a brain-machine interface was implemented and marketed in 2005, although it was limited to “yes” or “no” responses at that time. Furthermore, there is one area of research that does not exist but would be ideally studied using NIRS, and that is the development of social interaction and conversational skills. One recent study reports on correlations in NIRS data collected from two people playing a joint computer game (Cui, Bryant, & Reiss, 2012), using similar analysis techniques to the ones we evoked for the development of global networks. NIRS researchers are in a unique position to apply such methods to the study of natural communications, carried out in an ecological setting, whereby two or more people simply talk to each other face to face (while each wears a NIRS cap). Beyond the two-person hyper-scanning, NIRS would enable us to perform multi-person simultaneous recording, which may further reveal brain system for social communicative behavior in the real world. Apart from such pioneering use, traditional studies of human brain imaging will also move forward greatly with the advance of data analysis methods such as those for brain connectivity, and technical advances including the general use of high-density NIRS. In particular, further details of the neural substrates of language acquisition in infants and children will be unveiled in the future. Currently, fNIRS methodology is still developing with several limitations, as described in this chapter. We believe many of these problems will be overcome in the near future, and many more linguists and clinicians will start to use fNIRS for a broad range of applications, leading fNIRS to grow into a major technique in the cognitive neurosciences.

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CHAPTER 8

WHAT HAS DIRECT CORTICAL AND SUBCORTICAL ELECTROSTIMULATION TAUGHT US ABOUT NEUROLINGUISTICS?

HUGUES DUFFAU

INTRODUCTION

INVESTIGATING the neural basis of language is one of the most important challenges in neuroscience. The development of functional neuroimaging has allowed a noninvasive study of the organization of critical brain structures. Nonetheless, this technique still lacks reliability at the individual level, especially concerning language mapping in brain tumor patients, due to neurovascular uncoupling (Agarwal et al., 2016).

As a consequence, invasive electrophysiological methods are currently considered the "gold standard" for brain mapping. Extraoperative mapping using a subdural grid can also be achieved. Although this technique has been used extensively in epilepsy surgery because it also enables detection of seizure foci, only the cortex can be mapped: it provides no information about subcortical connectivity. Thus, in the past decade, a growing number of authors have advocated the use of direct electrical stimulation (DES) intraoperatively, especially in neuro-oncology, since glioma invades both cortical and subcortical structures (Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2015; Mandonnet, Capelle, & Duffau, 2006). Indeed, during brain surgery, it has become common clinical practice to awaken patients in order to assess the functional role of restricted cerebral regions. The surgeon can maximize the extent of resection, and thereby improve the overall survival, without eliciting permanent neurological impairment, owing to an individual mapping and preservation of critical structures. This means that the resection is achieved according to functional boundaries (Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Duffau, 2012a).

In practice, patients perform several sensorimotor, visuospatial, language, cognitive, or even emotional tasks while the surgeon temporarily interacts with discrete areas within the gray and white matters around the tumor, using DES (Figure 8.1). If the patient stops moving or speaking, or produces the wrong response, the surgeon avoids removing the stimulated site (Duffau, 2011a). Indeed, DES transiently

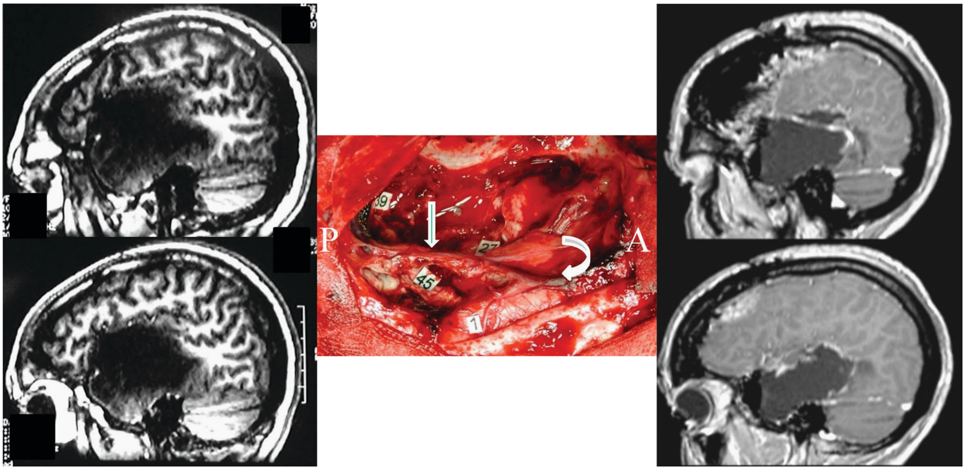

FIGURE 8.1. *Left*: Preoperative sagittal T1-weighted MRI showing a low-grade glioma involving the whole left dominant temporal lobe in a right-handed patient who experienced seizures, with a normal neurological examination.

Middle: Intraoperative photograph of the left hemisphere after surgical resection under local anesthesia, with the use of DES to map language both at cortical and subcortical levels. The number tags correspond to the critical areas detected by DES mapping, as follows: (1) ventral premotor cortex, eliciting anarthria when stimulated; (39) posterior portion of the inferior longitudinal fascicle, eliciting alexia when stimulated; (45) anterior part of the vertical (temporal) portion of the arcuate fascicle, eliciting phonemic paraphasia and repetition disorders during stimulation; (27) horizontal (temporal) part of the inferior fronto-occipital fascicle, eliciting semantic paraphasia during DES. All these eloquent structures have been preserved, due to representation of the functional boundaries of the resection.

Straight arrow: Labbe's vein; curved arrow: Sylvian fissure; A = anterior; P = posterior.

Right: Postoperative sagittal T1-weighted MRI showing an extensive resection of the left dominant temporal lobe, including the "Wernicke's area" (posterior part of the superior temporal gyrus beyond the Labbe's vein). Due to neuroplasticity mechanisms, and thanks to the preservation of the subcortical language connectivity, the neurological examination was normal after surgery, in particular with no language disturbances. The patient resumed a normal familial, social, and professional life.

interacts locally with a small cortical or axonal site, but also nonlocally, as the focal perturbation will indeed disrupt the entire subnetwork sustaining a given function (Mandonnet, Winkler, & Duffau, 2010). Thus, in contrast to functional neuroimaging, DES is able to detect the structures essential for brain functions, by inducing a transient virtual lesion based on the inhibition of a subcircuit during approximately 4 seconds—with the possibility to check whether the same functional disorders are reproduced when repeated stimulations are applied over the same area. Interestingly, by collating all cortical and axonal sites where the same type of errors are observed when stimulated, one can assemble the subnetwork of the disrupted subfunction. Consequently, DES represents a unique opportunity to identify with great accuracy (about 5 mm) and reproducibility, in vivo in humans, the structures that are crucial for cognitive functions, both at cortical and subcortical (white matter and deep gray nuclei) levels (Duffau, 2015). Combining transient disturbances elicited by DES with the anatomical data provided by pre- and postoperative MRI enables reliable anatomo-functional correlations, supporting a network organization of the brain (Duffau, 2014b), and leading to the reappraisal of cognitive models—notably those regarding language representation (Duffau, Moritz-Gasser, & Mandonnet, 2014).

In this chapter, the goal is to critically review the basic principles of DES, its advantages and limitations, and what DES can tell us about neural foundations of language, that is, the large-scale distribution of language areas in the brain, their connectivity, and their ability to reorganize—the so-called *neuroplasticity*.

Basic Aspects of DES

Principles of DES

The membrane potential (MP) of the neuron at rest varies between −60 and −100 millivolts (mV). The principle of electrical stimulation is to generate membrane excitability via an initial phase of passive modification of the local MP at the level of the cathode (i.e., the negative electrode). Here the inner side of the membrane becomes progressively less negative than the outer side (the membrane becomes inversely hyperpolarized with respect to the anode). The intensity of this phenomenon depends on the parameters of the stimulations and the characteristics of the membrane (Jayakar, 1993). The outer membrane can be more easily stimulated at the level of the initial segment of the axon, and at the level of the fibers that are myelinized and have a larger diameter (Ranck, 1981). If the MP reaches the liminar depolarization (i.e., threshold), a second phase occurs that begins with the opening of voltage-dependent ionic canals, which allows entry of Na+ ions, and therefore inverts the MP between +20 mV and +30 mV. A secondary output of K+ ions, associated with an inhibition of the entering flux of Na+ ions, brings the MP back to its resting state. Once generated, this rapid sequence of MP fluctuation—the action potential—is still the same, whatever the stimulation parameters are (law of "all or nothing").

Stimulation Parameters: Theoretical Approach

The first requirement for DES is that it must be entirely safe for the cerebral parenchyma. Nonetheless, it may generate a lesion by accumulating negative charge at the level of the cathode, or by producing metal ions at the level of the anode (Agnew & McCreery, 1987). The use of biphasic impulses eliminates these risks because the second stimulus phase inverts the effects of the first. Tissue damage can also be induced, on the one hand, by excessive heat, produced specifically by hydrolysis, which could cause vacuolization and chromatolysis; or, on the other hand, by "leakage" of the intracellular current, which goes from the anode to the cathode through the cytoplasm, posing a risk of lesions to the mitochondria and endoplasmic reticulum; or even by alteration of the homeostasis when the neurons are activated in a manner that is too repetitive and synchronous (Yeomans, 1990). These risks are directly linked to the density of the charge, and studies based on animal experiments have led to an upper threshold limit of 55 microcoulombs/cm^2/phase, at which no lesions were observed (Gordon et al., 1990). In theory, DES can also generate seizures, even though the rate of intraoperative epilepsy is basically nil in teams with experience (Deras et al., 2012). Nonetheless, in case of seizures, irrigation of the cortex with cold serum allows an interruption of the crisis in a few seconds (Sartorius & Berger, 1998).

The second requirement for DES is that it should induce a reproducible response when applied to neural structures. The relationship between stimulation parameters and tissue-response characteristics can be summed up by the intensity/duration curve, in which the intensity of the current is recorded as a function of the duration of the impulse (Jayakar, Alvarez, Duchowny, & Resnick, 1992). The *rheobasis* is thus defined as the minimal intensity required to generate an action potential at elevated values of impulse duration. *Chronaxie* is the impulse duration required to elicit a response when the stimulus intensity is twice the rheobasis. The chronaxie corresponds to the point on the intensity/duration curve where the energy allowing an action potential to be generated is minimal, for a charge twice the minimum charge: this is the optimal stimulation point (best benefit/risk ratio).

The chronaxie point depends on the characteristics of the tissue being stimulated, specifically on its impedance. The few studies on this topic (Geddes & Baker, 1967) have produced resistance values of 250 Ohms for gray matter, 500 Ohms for white matter, and 65 Ohms for cerebrospinal fluid (Nathan, Lesser, & Gordon, 1993). Moreover, chronaxie can be significantly modified by the degree of cerebral maturation, notably by myelinization. In this way, chronaxie of non-myelinized nerve fibers is considerably longer (0.4–3.5 ms) than that of the myelinized axons (0.05–0.4 ms) (Jayakar et al., 1992). The size of the fiber also seems to be a factor, in that the axons of greater diameter are more readily excited (Ranck, 1981). Moreover, impedances can be modified by the state of the patient (awake or under general anesthesia). Finally, any pathological process, whether lesional (tumor) or non-lesional (epilepsy, postictal status), can interfere directly with the tissue's excitability (Jayakar, 1993).

As regards the frequency of electrical impulses, myelinized axons produce a single response for each stimulation delivered between 50 and 100 Hz (Jayakar, 1993). A neural membrane is, in fact, refractory to all stimuli lasting 0.6 milliseconds (ms) to 2 ms following an action potential. This status precedes a second phase of transitory hyperexcitability, during which the tissue could be stimulated by less intense currents than during the initial stimulus, but the risk of seizure is increased.

Moreover, when the neural structures are kept in a state of infra-liminar depolarization, the threshold required to generate the impulse increases; this phenomenon is known as *accommodation*. Accommodation occurs if the MP changes quite progressively, which may be observed when sinusoidal impulses are used. This is the reason why rectangular impulses are recommended for stimulations.

Although two electrodes are still required to produce a current, the stimulations are considered to be "monopolar" if only one of the electrodes is "active" (in general, the cathode), that is, localized in relation to the target tissue, while the reference electrode (in general, the anode) is located at a distance. Whereas the current density is distributed in a relatively uniform manner around the electrode, each tissue located in the current's pathway can nevertheless be stimulated, especially if its depolarization threshold is less than the target threshold. To reduce this risk of a false positive, it is preferable to use a bipolar stimulation, that is, where the cathode and the anode are both "active," or in other words, both are located at the level of the target tissue (Nathan et al., 1993). Only structures located between the two electrodes are stimulated in this way, so there is less risk of diffusion and therefore a greater precision (Haglund, Ojemann, & Blasdel, 1993). Nevertheless, because current distribution is more complex with bipolar stimulation than with monopolar stimulation, it is more difficult to build a model in order to choose optimal parameters for achieving the most reproducible responses (Nathan et al., 1993), especially in view of the overlapping of effects at the cathode (depolarization state of the level of peri-cathodic tissues) and the anode (hyperpolarization state at the level of peri-anodic tissues). It is recommended to use biphasic impulses to compensate for this limitation (Jayakar, 1993).

Finally, a recent computational study has suggested that directing the bipolar electrodes orthogonal (and not parallel) to the axis of a white matter fascicle should facilitate its identification, as the chances are higher in this configuration that at least one of the electrode tips will be in contact with the tract (Mandonnet & Pantz, 2011).

Stimulation Parameters: Practical Approach

In practice, bipolar electrode tips that are spaced 5 millimeters (mm) apart and that deliver a biphasic current (pulse frequency 60 Hz, single-pulse phase duration 1 ms, and intensity from 6 to 18 mA under general anesthesia or from 2 to 6 mA under local anesthesia) are applied to the brain (Duffau, 2004, 2007). DES allows the mapping of motor function (by inducing involuntary motor response if the stimulation is applied at the level of a motor site, or by eliciting arrest of movement when stimulating the negative motor network), somatosensory function (by eliciting dysesthesia described by the patient himself intraoperatively), and cognitive functions such as language (spontaneous speech, counting, picture naming, comprehension, reading, writing, bilingualism, etc.), calculation, memory, visuospatial processing, judgment, or even mentalizing (Fernandez-Coello et al., 2013). Patients are awake, and transient disturbances are generated by applying DES at the level of a functional "epicenter" (Ojemann, Ojemann, Lettich, & Berger, 1989). A speech therapist or neuropsychologist must be present in the operating room, in order to accurately interpret the kind of disorders induced by DES, for instance, speech arrest, anarthria, speech apraxia, phonological disturbances, semantic paraphasia, perseveration, anomia, dyscalculia, alexia, and so on. Thus, DES is able to identify in real time the cortical sites *essential for the function* before beginning the resection, in order to both select the best surgical approach and define the cortical limits of the resection (Duffau, 2005a, 2011a) (Figure 8.1).

In addition, DES also allows the identification and preservation of subcortical pathways crucial for sensorimotor, visuospatial, language, and other cognitive functions (Duffau et al., 2002; Duffau et al., 2003a; Duffau, 2015; Thiebaut de Schotten et al., 2005). Indeed, it allows the study of the anatomo-functional connectivity by directly and regularly stimulating the white matter tracts throughout the resection, and by eliciting a functional response when in contact with the essential eloquent fibers, according to the same principle as that described at the cortical level. Thus, it is important that the patient remains awake during the entire removal of the tumor, and not only for the initial stage of cortical stimulation. This is why intraoperative cortico-subcortical stimulation is time-consuming, and why the number of tasks during surgery are limited by the progressive tiredness of the patient.

Strengths of DES: A Door into Neural Networks

One of the major advantages of DES is that it intrinsically does not cause any false negatives. Indeed, each critical structure, whatever its actual role in brain function, will be electrically disturbed by DES, which necessarily will induce a functional consequence. This optimal sensitivity explains why DES is currently considered the gold standard in brain mapping. First, intraoperative DES enables neurosurgeons to tailor the resection according to functional boundaries, thus minimizing the risk of permanent deficit while preserving the patient's quality of life (Duffau, 2012a). Second, DES is used to validate the noninvasive methods of functional neuroimaging (functional magnetic resonance imaging [fMRI] and magnetoencephalography [MEG]) (Giussani et al., 2010; Korvenoja et al., 2006; Roux et al., 2003) as well as diffusion tensor imaging (DTI) (Kinoshita et al., 2005; Leclerq et al., 2010). Indeed, the reliability of fMRI has been estimated at only 60%–70%, both in healthy subjects (Havel et al., 2006) and in patients with cerebral tumors (Giussani et al., 2010; Roux et al., 2003). Recently, by comparing preoperative language (fMRI; see Heim & Specht, Chapter 4 in this volume) with intraoperative electrical stimulation mapping, Kuchsinski et al. (2015) calculated the sensitivity of fMRI at 37.1% and the specificity at 83.4%. In addition, functional neuroimaging is not able to differentiate those areas *essential* for function from those that can be compensated while activated during a task. For example, glioma involving the supplementary motor area can be surgically excised without generating any permanent neurological deficit due to the recruitment of the contra-lateral homologous region (Krainik et al., 2004), even though this supplementary motor area was detected on preoperative fMRI in patients performing language tasks (Krainik et al., 2003). Finally, functional neuroimaging is able to map the gray matter but not the white matter tracts.

The recent development of DTI, enabling a tractography of white matter tracts in vivo, has provided new insights into cerebral connectivity (Catani, Jones, & Ffytche, 2005; see Catani & Forkel, Chapter 9 in this volume). However, it is noteworthy that recent review articles by DTI experts have underlined the need for a rigorous anatomical validation (Hubbard & Parker, 2009; Jbabdi & Johansen-Berg, 2011; Le Bihan, Poupon, Amadon, & Lethimonnier, 2006). Indeed, DTI does not directly reflect cerebral functional reality, but provides a very indirect approximation based on biomathematic reconstructions—explaining why results may vary depending on the model used to analyze the MRI data (Duffau, 2014a; Kinoshita et al., 2005; Pujol et al., 2015). Correlation studies between tractography and intraoperative direct subcortical electrostimulation have shown concordance in only 82% of cases (Leclerq et al., 2010). Moreover, DTI provides anatomical but not functional information about the white matter pathways. As a consequence, DES is a unique tool to better understand the organization of networks underpinning brain processing (Duffau, 2014)—especially language (see later discussion).

With regard to the spatial resolution, although it has been argued that the currents delivered by the tips of the bipolar electrodes can diffuse over the cortex, thus limiting the spatial accuracy of the tested areas, it is necessary to distinguish two types of *diffusion*. The first one involves the spread of the depolarizing electric field over the cortical surface. It was demonstrated using optical imaging that the spatial area affected by this spreading diffusion is about 5 mm in diameter (Haglund et al., 1993). The diffusion has not been investigated experimentally for axonal stimulations, but theoretically, it should be of the same order, or even smaller when the bipolar electrode is parallel to the direction of the fascicle (Mandonnet & Pantz, 2011). Thus, the spatial resolution of DES is about 5 mm, namely less than the 1 centimeter (cm) spacing of subdural strip and grid electrodes used for recording epileptiform activity and for cortical mapping before epilepsy surgery.

The second type of diffusion refers to the biological and physiological *propagation* of the stimulation. Indeed, when stimulating the cortical or the axonal part of the neuron, the action potential is further transmitted by the physiological conduction along the axon, and consequently, neurons at the end of the axons can be stimulated by these presynaptic currents. So, in essence, DES is highly nonlocal: it interacts with the entire network that sustains a function. The stimulated point (axonal or cortical) is only an input gate to this entire network (Mandonnet et al., 2010).

Since DES allows the performance of online, anatomo-functional correlations at both cortical and subcortical levels, and since each eloquent discrete site identified is only an input gate to a wider functional network, DES is consequently a perfect tool for the study of spatiotemporal brain connectivity. For a long time, however, DES was considered a method that could only detect cortical "epicenters," and thus useful for mapping only gray matter (Ojemann et al., 1989). In fact, intraoperative DES offers the unique opportunity to directly access not only the functional cortical organization, but also the effective connectivity—that is, the influence that a cerebral region may have on another region (Lee, Friston, & Horwitz, 2006). Indeed, it is now well known that to generate a function, it is necessary that several areas work together. Specific temporal dynamics allow synchronization within the distributed networks (Bartels & Zeki, 2005; McClelland & Rogers, 2003). This explains why lesions involving the white matter very frequently induce severe and permanent deficits, as demonstrated in stroke studies (Catani & Ffytche, 2005). It is thus likely that subcortical DES induces the same effect as a transient virtual lesion, which disrupts the electrical connectivity between brain regions that normally communicate to generate the function. This hypothesis is supported by the fact that the DES of main pathways has the same functional consequence as a disconnection syndrome, for instance, conduction aphasia during stimulation of the left arcuate fascicle (Duffau et al., 2002; Maldonado, Moritz-Gasser, & Duffau, 2011), or semantic disturbances during stimulation of the left inferior fronto-occipital fascicle (Duffau et al., 2005; Moritz-Gasser, Herbet, & Duffau, 2013). Furthermore, beyond such an inhibition elicited within long-range cortico-cortical networks, DES may also generate a virtual disconnection within the cortico-subcortical loops, as demonstrated by the induction of transcortical motor aphasia during stimulation of the left dominant frontostriatal tract—which connects the supplementary motor area and the cingulum with the head of the caudate nucleus (Duffau et al., 2002; Kinoshita et al., 2015). It is worth noting that the possibility of obtaining these very precise anatomo-functional correlations supports the fact that DES propagates in a "subcircuit" rather than in the entire language network, since stimulation can inhibit only a specific component of language (e.g., phonology, semantics, or syntax). Finally, this unifying vision of network stimulation can contribute to understanding why conduction aphasia can be observed for subcortical (Duffau et al., 2002) as well as cortical stimulation (Quigg & Fountain, 1999; Quigg, Geldmacher, & Elias, 2006): the same network is disrupted, with an input either subcortical or cortical.

This view also agrees with works using implanted grids for pre-surgical planning of medication-resistant epileptic patients. It has been shown that the stimulation of a cortical site induces a signal in a distant (but axonally linked) area (i.e., the so-called *cortico-cortical evoked potential*; Yamao et al., 2014). This concept is also very similar to deep brain stimulation of the basal ganglia. Indeed, it is now widely accepted that stimulation of the subthalamic nucleus also interacts with the entire network of the basal ganglia (McIntyre, Savasta, Walter, & Vitek, 2004; Montgomery, 2004), including the primary motor cortex and its feedback loops. From a practical point of view, this understanding suggested new targets in neuromodulation for Parkinson's disease, such as the primary motor area (Cilia et al., 2007; Pagni et al., 2005). Theoretically, these networks are modeled as interacting nonlinear dynamic systems, and pathological states can be associated with abnormal locking in a strongly synchronized state, leading to proposals for new schemes of stimulation (Popovych, Hauptmann, & Tass, 2006; Rosenblum & Pikovsky, 2004). Such bio-mathematical modeling may also explain how DES actually *induces* functional disturbance.

On the other hand, diffusion within a large-scale network may also represent a limitation of DES, as discussed in the next section.

WEAKNESSES OF DES

False Negatives

It is important to stress that the slightest technical mishap can result in false negatives. Indeed, it was previously explained that an intensity of stimulation that is too low, that is of too short duration, or that is performed during a transient post-epileptic refractory phase, may lead to an erroneous "negative mapping" (Taylor & Bernstein, 1999). Nevertheless, such failure can be avoided by strictly following the theoretical and practical rules of stimulation.

A subtler limitation would be an inappropriate functional task selection. For instance, if intraoperative testing is based only on a visual-naming task, word-finding difficulties can arise after resection of the posterior superior temporal gyrus, due to the anatomic dissociation of visual and auditory naming (Hamberger, McClelland, McKhann, Williams, & Goodman, 2007). Repetition tasks should be added for lesions involving this same region (Quigg & Fountain, 1999; Quigg et al., 2006). In addition, patients who undergo operations for a tumor within the left dominant hemisphere may exhibit postoperative working memory deficits, despite extensive intraoperative language mapping (du Boisgueheneuc et al., 2006; Teixidor et al., 2007). This is a result of the nonspecific engagement of working memory by tasks adopted during surgery. Thus, the erroneous conclusion is drawn that the tissue is "not functional"—which may have been true for language only. Specific testing of spatial awareness is also mandatory during surgery within the right "non-dominant" hemisphere in order to avoid any postoperative hemineglect (Thiebaut de Schotten et al., 2005). Thus, the limited number of feasible intraoperative tasks can limit function detection. Thus it is important to optimize the selection of the intrasurgical tests for each patient on the basis of the preoperative functional assessment from both extensive neurological and neuropsychological examinations (Fernandez-Coello et al., 2013).

False Positives

Although the sensitivity of intraoperative electrical mapping is very high, its specificity remains a matter of debate. First, the patient's tiredness after approximately one to two hours of continuous functional assessment during an awake procedure may induce a decline of accuracy and rapidity of response. It could become difficult to differentiate the immediate proximity of the eloquent structures (transient deficit during DES) from the tiredness of the patient. Second, DES may induce partial seizures that can look like a "positive effect" of the stimulation. For example, a partial seizure elicited by DES may generate a transient language disorder after stimulation within the dominant hemisphere, creating the wrong impression that this area is crucial for the function. A rigorous methodology of stimulation, as detailed in the preceding, will avoid such false positives. Above all, the reproducibility of the symptoms elicited by DES during initial cortical mapping needs to be confirmed by subcortical mapping. The coherency of the two maps will ensure that the organization of the network (and not only isolated epicenters) has been correctly understood. Third, while there is no cortical spreading of DES, there is a propagation of the stimulation along the axon within a network wider than the sole area tested. Although this property allows the study of connectivity with a very high sensitivity, it can also lead to false positives. Indeed, it has been reported that when electrical mapping was performed using subdural grids for preoperative planning in chronic epilepsy, DES of a cortical site elicited a signal in a remote but axonally linked region (Ishitobi et al., 2000). Such mechanisms, especially if the stimulation generates a backward propagation, might explain observations that resections of "positive" areas did not cause postoperative deficits—such as the left basal temporal area (Lüders et al., 1991).

WHAT DES CAN TELL US ABOUT THE NEURAL BASIS OF LANGUAGE: RETHINKING MODELS OF PICTURE NAMING

Bilateral Probabilistic Map of Eloquent Cortical Areas Detected by DES: Broca's Area Revisited

One of the best examples of a language circuit that should be well understood is the network underlying picture naming. Indeed, DES has allowed a re-examination of the classical Broca-Wernicke's model, which took precedence over all others for many

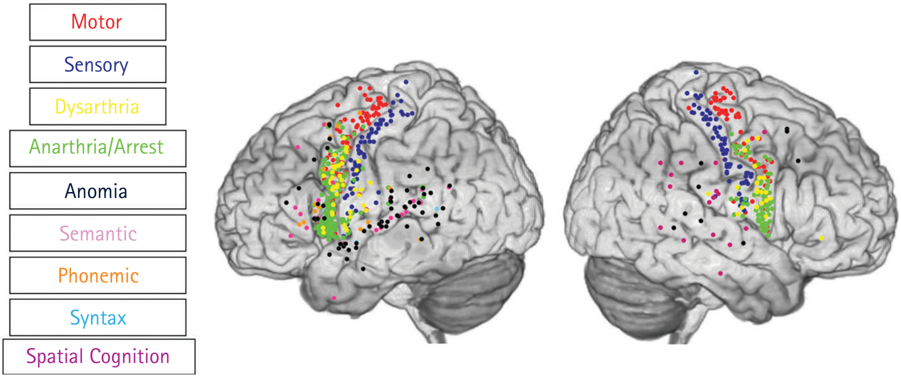

FIGURE 8.2. Probabilistic map of critical functional regions of the human cortex in the left and right hemispheres, issued from DES in awake patients performing sensorimotor, language, and line bisection tasks.

Source: Modified from Tate et al. (2014).

decades. A recent study performed in 165 consecutive patients who underwent awake surgery with the use of intraoperative DES provided the first bilateral probabilistic map for essential cortical functions in the left and right hemispheres of humans (Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2014). Stimulation sites eliciting positive (sensory/motor) or negative (speech arrest, dysarthria, anomia, phonological or semantic paraphasias, syntactic disorders, hemineglect) findings in patients who performed counting, picture naming, and line bisection tasks were recorded and mapped onto a standard Montreal Neurologic Institute (MNI) brain atlas. Compilation of all stimulation data (*n* = 771 stimulation sites) demonstrated the wide bilateral distribution of cortical representation within and between critical functions (Figure 8.2). In particular, it was demonstrated that speech arrest during DES was localized to ventral premotor cortex, not the classical Broca's area (Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2015). In addition, anomia/paraphasia data demonstrated foci not only within classical Wernicke's area, but also within the middle and inferior frontal gyri. Therefore, these data challenge classical theories of brain organization (e.g., Broca's area as speech output region) and provide a distributed framework for future studies of language networks (Tate et al., 2014).

The Network Underpinning Picture Naming: Lessons from DES

According to the revisited model of picture naming issued for DES (Duffau et al., 2014) (Figure 8.3), in the naming process, the first step is visual perception and recognition. DES of the optic pathways may elicit reversible phosphenes or visual loss in the contralateral visual field (described by the awake patients) due to an inhibition of visual

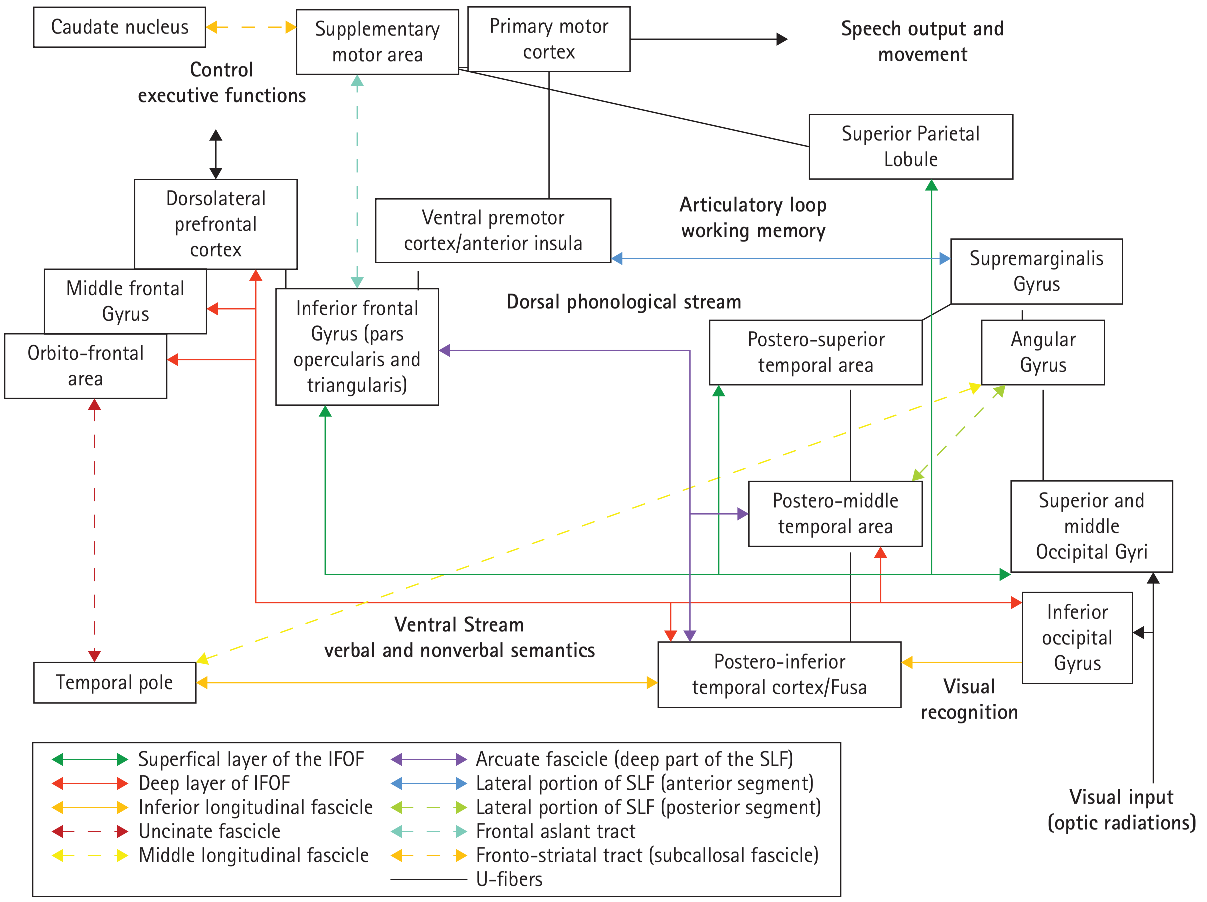
Caudate nucleus
Supplementary motor area
Primary motor cortex
Speech output and movement
Control executive functions
Superior Parietal Lobule
Dorsolateral prefrontal cortex
Ventral premotor cortex/anterior insula
Articulatory loop working memory
Supramarginalis Gyrus
Middle frontal Gyrus
Inferior frontal Gyrus (pars opercularis and triangularis)
Dorsal phonological stream
Postero-superior temporal area
Angular Gyrus
Orbito-frontal area
Postero-middle temporal area
Superior and middle Occipital Gyri
Inferior occipital Gyrus
Ventral Stream verbal and nonverbal semantics
Temporal pole
Postero-inferior temporal cortex/Fusa
Visual recognition
Visual input (optic radiations)
Superfical layer of the IFOF
Deep layer of IFOF
Inferior longitudinal fascicle
Uncinate fascicle
Middle longitudinal fascicle
Arcuate fascicle (deep part of the SLF)
Lateral portion of SLF (anterior segment)
Lateral portion of SLF (posterior segment)
Frontal aslant tract
Fronto-striatal tract (subcallosal fascicle)
U-fibers

FIGURE 8.3. Proposal of a new model of connectivity underlying language processing and its relationships with cognitive functions, with incorporation of anatomic subcortical constraints, elaborated on the basis of structural-functional correlations provided by intraoperative DES combined with perioperative neuroimaging.

Source: Modified from Duffau et al. (2014).

perception (Gras-Combes, Moritz-Gasser, Herbet, & Duffau, 2012). Visual formal paraphasia has also been evoked by electrical interferences with a second stage of visual processing (i.e., visual recognition). These disorders have been generated by axonal DES of a subpart of the posterior inferior longitudinal fascicle (ILF), which links the visual cortex with the "visual object form area" (Mandonnet, Gatignol, & Duffau, 2009; Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015). This area, participating in object recognition, is close to the visual word form area, which receives another subpart of the ILF as afference, a subpathway involved in reading—thus generating alexia when damaged (Gaillard et al., 2006; Zemmoura et al., 2015). Furthermore, by performing subcortical DES of distinct subcomponents within the left occipito-temporal white matter, a double dissociation between alexia (lower fibers) and anomia (upper fibers) has been generated in the same patients (Chan-Seng, Moritz-Gasser, & Duffau, 2014; Gil Robles et al., 2013). Thus, these data support the existence of parallel pathways coming from the occipital cortex, specifically involved in word versus object recognition.

Following this first step of visual recognition, a dual model for visual language processing was proposed on the basis of DES findings, with a ventral stream involved in mapping visual information to meaning (the "what" pathway) and a dorsal stream dedicated to mapping visual information to articulation through visuo-phonological conversion—completing the model proposed by Hickok and Poeppel (2004; see Hickok, Chapter 20 in this volume), which nonetheless did not take into account anatomic constraints, especially with regard to white matter tracts. Because double dissociations between phonemic and semantic errors have been demonstrated by DES (Maldonado et al., 2011), both processes seem to be performed in parallel, and not serially. Indeed, concerning the ventral semantic stream, cortically, semantic paraphasias have been induced by DES along the posterior part of the superior temporal sulcus, in the dorsolateral prefrontal cortex, and in the pars orbitaris of the inferior frontal gyrus (Duffau et al., 2005; Tate et al., 2014). Axonally, such disturbances were generated by stimulation of the left inferior fronto-occipital fascicle (IFOF), a pathway that connects the posterior occipital lobe and visual object form area to anterior cortical frontal areas, including the inferior frontal gyrus and dorsolateral prefrontal cortex (Martino, Brogna, Gil Robles, Vergani, & Duffau, 2010; Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013)—known to be involved in language semantics and higher cognitive functions as multimodal integration or judgment (Duffau et al., 2005; Moritz-Gasser et al., 2013; Plaza, Gatignol, Cohen, Berger, & Duffau, 2008). Therefore, pretreated information by the visual recognition system is subsequently processed by the semantic system (in parallel to the dorsal phonological stream, see later discussion) before being processed by the executive system. In addition to this direct ventral route subserved by the IFOF, there is an indirect ventral semantic pathway with a relay at the level of the temporal pole, which represents a semantic "hub" allowing integration of the multimodal data coming from the unimodal systems (Holland & Lambon-Ralph, 2010). This indirect ventral stream is constituted by the anterior part of the ILF, connecting the visual object form area with the temporal pole (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007), and then relayed by the uncinate fascicle, which links the temporal pole with the pars orbitaris of the inferior frontal gyrus (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Duffau, Herbet, & Moritz-Gasser, 2013).

Regarding the dorsal phonological stream, cortically, phonemic paraphasia can be elicited by DES of the inferior parietal lobule and inferior frontal gyrus (Maldonado et al., 2011; Tate et al., 2014). Axonally speaking, phonemic paraphasias and repetition disorders are elicited when stimulating the arcuate fascicle (Maldonado et al., 2011), which is a fiber tract stemming from the caudal part of the temporal lobe, mainly the inferior and middle temporal gyri, that arches around the insula and advances forward to end within the frontal lobe, essentially within the ventral premotor cortex and pars opercularis of the inferior frontal gyrus (Duffau et al., 2002; Martino et al., 2013). Geschwind (1970) has previously postulated that lesions of this tract would produce conduction aphasia, including phonemic paraphasia, supporting the role of the subpart of the dorsal stream mediated by the arcuate fascicle in phonological processing. Interestingly, the posterior cortical origin of this tract within the posterior part of the inferior temporal gyrus corresponds to the visual object form area (Martino et al., 2013). Indeed, this region represents a functional hub, involved both in semantic (see earlier discussion) and phonological processing dedicated to visual material (Vigneau et al., 2006). Thus, phonological processing subserved by the arcuate fascicle is performed in parallel to the semantic processing undertaken by the ventral route. In addition to this direct dorsal route, tractography studies show the existence of an indirect dorsal stream, running more superficially, and undertaken by the lateral superior longitudinal fascicle (Catani et al., 2005). This pathway is implicated in articulation and phonological working memory, as demonstrated by DES. Cortical areas eliciting articulatory disorders are located essentially in the ventral premotor cortex, and also in the supramarginal gyrus and posterior part of the superior temporal gyrus (Duffau et al., 2003b; Tate et al., 2014). Axonally, stimulation of the white matter under the frontoparietal operculum and supramarginal gyrus, laterally and ventrally to the arcuate fascicle, induces anarthria as well (van Geemen, Herbet, Moritz-Gasser, & Duffau, 2014). Indeed, this lateral operculo-opercular component of the superior longitudinal fascicle constitutes the articulatory loop, by connecting the supramarginal gyrus/posterior portion of the superior temporal gyrus (which receives feedback information from somatosensory and auditory areas) with the frontal operculum (which receives afferences bringing the phonological/phonetic information to be translated into articulatory motor programs and efferences toward the primary motor area; Duffau et al., 2003b).

To sum up, DES has resulted in the elaboration of a new model of picture naming, based on multiple direct and indirect cortico-subcortical interacting subnetworks involved in semantic, phonological, and articulatory processes. This model offers several advantages in comparison with previous ones: (1) it explains double dissociations during DES (e.g., semantic versus phonemic paraphasias); (2) it takes into account the cortical and subcortical anatomic constraints; (3) it explains the possible recovery of aphasia following a lesion within the "classical" language areas (see the following discussion).

Other Language Aspects: New Insights Provided by DES

Using the same paradigm, DES has allowed a reappraisal of cognitive models underlying other language aspects. For instance, DES has demonstrated that syntactic processing was subserved by de-localized cortical regions (left inferior frontal gyrus and posterior middle temporal gyrus) connected by a subpart of the left inferior superior longitudinal fascicle. Interestingly, this subcircuit is interacting but independent of the subnetwork involved in naming, as demonstrating by double dissociation between syntactic (especially grammatical gender) and naming processing during DES. These findings support parallel rather than serial theory, calling into question the principle of the "lemma" (Vidorreta, Garcia, Moritz-Gasser, & Duffau, 2011).

In connectionist views of brain organization, interactions between different systems have also been described. For instance, a recent DES study demonstrated that the dorsal phonological pathway, supported by the left arcuate fascicle/superior longitudinal fascicle complex subcortically, is crucial to accurate word repetition (Moritz-Gasser & Duffau, 2013). It enables the conversion of auditory input, processed in the verbal working memory system, into phonological and articulatory-based representations. Although this contribution is essential, the ventral semantic pathway, connected by the left IFOF, also contributes to word repetition of real words or pseudo-words. Indeed, perioperative and intraoperative language evaluations of glioma patients undergoing awake surgery highlight the strong interaction of both pathways in word repetition in order to convert auditory input into articulatory output efficiently (Moritz-Gasser & Duffau, 2013).

DES also has showed the existence of an executive system (including prefrontal cortex, anterior cingulum, and caudate nucleus) involved in the cognitive control of more dedicated subcircuit as language switching—itself constituted by a wide cortico-subcortical network comprising posterior temporal areas, supramarginal and angular gyri, inferior frontal gyrus, and a subpart of the superior longitudinal fascicle (Moritz-Gasser & Duffau, 2009). In addition, it seems that the frontal aslant tract, which connects the pre-supplementary motor area and anterior cingulate with the inferior frontal gyrus (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012), might play a role in the control of language, especially with regard to planning of speech articulation (Kinoshita et al., 2015). Indeed, stimulation of this pathway may induce stuttering (Kemerdere et al., 2016). In the same vein, a cortico-subcortical loop involving the deep grey nuclei, especially the caudate nucleus, was also demonstrated as participating in the control of language (selection/inhibition), since DES of the head of the caudate nucleus in the left hemisphere generated perseverations with a high level of reliability (Gil Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005). This cortico-striatal loop could be anatomically supported by the fronto-striatal tract (Kinoshita et al., 2015).

Furthermore, by using a semantic association task (e.g., Pyramids and Palm Tree Test; Howard & Patterson, 1992), it was reported that DES of a wide subnetwork comprising the left postero-superior temporal area, dorsolateral prefrontal cortex, and IFOF generated disturbances of comprehension, including verbal and nonverbal semantic processing as well as cross-modal judgment (Gatignol, Capelle, Le Bihan, & Duffau, 2004; Moritz-Gasser et al., 2013; Plaza et al., 2008). Interestingly, a double dissociation between picture naming and comprehension has been observed during DES, again supporting parallel subnetworks rather than serial processing (Duffau et al., 2013; Duffau et al., 2014). Of note, in this framework, the exact role of the middle longitudinal fascicle remains unclear (de Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011). The next step is to use DES to explore cortico-subcortical circuits involved in verbal and nonverbal working memory and attention, with a likely implication of a frontoparietal loop subserved by the lateral part of the superior longitudinal fascicle (Moritz-Gasser & Duffau, 2013), in emotional processing such as theory of mind and mentalizing (Herbet et al., 2014a; Herbet, Lafargue, Moritz-Gasser, Bonnetblanc, & Duffau, 2015), and even in consciousness (Herbet et al., 2014b; Herbet, Lafargue, & Duffau, 2016; Moritz-Gasser et al., 2013).

To sum up, our vision of the neural basis of language has begun to shift. For a long time, language was conceived in associationist terms of centers and pathways, the general assumption being that information is processed in localized cortical regions with the serial passage of information between regions accomplished through white matter tracts. Currently, an alternative *hodotopical* account is proposed, in which brain function is conceived as resulting from parallel distributed processing performed by distributed groups of connected neurons rather than individual centers (Duffau, 2008, 2014b). Conversely to serial models in which one process must be finished before the information proceeds to another level of processing, these new models of "independent networks" state that different processing can be performed simultaneously with interactive feedback. A multimodality approach seems now mandatory, with a more accurate analysis of the interactions between the subnetworks underlying distinct cognitive functions (e.g., language, visuospatial components, executive functions, as well as behavioral aspects) in order to open new avenues to better understand brain connectivity or "connectomics" (Duffau, 2015) (Figure 8.3).

DES AS A TOOL TO INVESTIGATE THE REORGANIZATION OF LANGUAGE CIRCUITS

As mentioned, in this hodotopical framework, brain functions are supported by extensive circuits comprising both the cortical epicenters (*topos*, i.e., sites) and connections between these "nodes," created by associating bundles of white matter (*hodos*, i.e., pathways) (De Benedictis & Duffau, 2011). Neurological function comes from the synchronization between different epicenters, working in phase during a given task, and explaining why the same node may take part in several functions depending on the other cortical areas with which it is temporarily connected at any one time. In this connectionist model that challenges the traditional localizationist philosophy, the central nervous system is organized into parallel networks that are dynamic, interactive, and able to compensate for each other—at least to a certain extent (Duffau, 2014b). In other words, language maps may be reorganized within remote networks, making neuroplasticity mechanisms possible, both ontogenetically (developmental learning) and after brain injury (Duffau, 2005b, 2006). Interestingly, in patients with slow-growing tumors such as diffuse low-grade gliomas, DES has demonstrated massive language reshaping, which allowed wide surgical resection of brain regions conventionally deemed to be inoperable on the basis of a rigid view of cerebral processing (Desmurget, Bonnetblanc, & Duffau, 2007). For example, extensive excisions of tumors infiltrating Broca's area in the left hemisphere have been carried out without causing permanent neurological deficit (Duffau, 2012b; Benzagmout, Gatignol, & Duffau, 2007). Indeed, resection of the pars opercularis and/or pars triangularis of the left inferior frontal gyrus is possible without risking aphasia, because, as already mentioned, Broca's area is not the final common pathway for speech (Tate et al., 2014; Tate et al., 2015). In addition, this area can be compensated by recruitment of adjacent regions, primarily the ventral premotor cortex (the crucial epicenter for speech articulation), and the pars orbitalis of the inferior frontal gyrus, the dorsal lateral prefrontal cortex, or the insula (Benzagmout et al., 2007; Duffau, 2012b). In the same vein, removal of gliomas infiltrating Wernicke's area also can be considered without eliciting permanent language disorders (Figure 8.1). Once again, the language compensation following resection of the postero-superior part of the left temporal lobe (and its junction with the inferior parietal lobule) can be explained by the organization of this complex function into remote networks. As a result, in addition to recruiting areas immediately around the lesion, reorganization may also involve remote lesions in the left hemisphere (particularly the supramarginal gyrus and also the pars triangularis of the inferior frontal gyrus), as well as contralateral sites in the right hemisphere because of transcallosal disinhibition—as demonstrated by combining intraoperative DES with perioperative functional neuroimaging (Sarubbo, Le Bars, Moritz-Gasser, & Duffau, 2012). Above all, subcortical connectivity should be obligatorily preserved to avoid aphasia.

Indeed, although a huge plastic potential has been demonstrated at the cortical level, subcortical plasticity is low, implying that axonal connectivity should be preserved to allow post-lesional compensation. Lessons from stroke studies have taught us that damage to the white matter pathways generate a more severe neurological impairment than lesions of the cortex. Recently, the elaboration of a probabilistic atlas computed on a series of patients who underwent resection for a glioma on the basis of intraoperative DES was proposed (Herbet, Maheu, Costi, Lafargue, & Duffau, 2016; Ius, Angelini, de Schotten, Mandonnet, & Duffau, 2011). The anatomo-functional correlations obtained by combining the intrasurgical functional data with postoperative anatomical MRI findings provided new insights into the potentials and limitations of cerebral plasticity. This probabilistic atlas highlighted the crucial role of the axonal pathways, namely, the connectome, in the reorganization of the brain after a lesion. It provided a general framework to establish anatomo-functional correlations by computing, for each brain voxel, its probability to remain intact—due to its functional role—on the postoperative MRI. Its overlap with the cortical MNI template and a DTI atlas offered a unique tool to analyze the potentialities and the limitations of inter-individual variability and plasticity, both for cortical areas and axonal pathways. As a rule, a low probability of residual tumors was observed on the cortical surface, whereas most of the regions with high probability of residual tumor were located in the deep white matter. Thus, projection and association axonal pathways seem to play a critical role in the proper functioning of the brain, especially the arcuate fascicle, superior longitudinal fascicle, and IFOF. In other words, language function subserved by long-range axonal pathways seems to be less subject to inter-individual variability and reorganization than cortical sites (Duffau, 2009; Herbet, Maheu, et al., 2016; Ius et al., 2011). The reproducibility of these results may suggest the existence of a “minimal common brain” necessary for basic cognitive functions such as language—even if insufficient for more complex functions such as multi-processing.

Because of this limitation of neuroplasticity due to the connectome, DES has great value for investigating brain processing, even though stimulation is by definition performed in patients with cerebral lesions. Indeed, if we admit that plasticity enabled the compensation of all areas involved by the tumor, it would not be possible to identify crucial epicenters in a probabilistic map based on glioma patients—as nonetheless done by Tate et al. (Tate et al., 2014; Tate et al., 2015). Thus, the ability to detect critical epicenters with a high rate of probability by inducing a reproducible deficit during intraoperative DES (such as anarthria during stimulation of the vPMC), despite cerebral reshaping, has significant implications for understanding the normal functional anatomy of the brain (Duffau, 2011b). In fact, the crucial cortical language (phonemic, semantic) epicenters detected by intraoperative electrical mapping in the study by Tate et al. (2014), involving glioma patients, correlate well with results provided by fMRI, extensively described in a meta-analysis extracted from 129 scientific reports (with 730 activation peaks) that investigated language using functional neuroimaging in healthy volunteers (Vigneau et al., 2006). Of note, these good correlations between DES and fMRI are only observed when comparing statistical maps, while only poor correlations are found at the individual level (see earlier discussion), explaining why DES remains the gold standard for a given patient.

Conclusion

DES represents a unique opportunity to identify with great accuracy, reproducibility, and reliability, in vivo in humans, the cortical and subcortical structures that are indispensable to the function, especially language, by inducing a transient virtual lesion based on the inhibition of a subcircuit over a few seconds. Currently, this is the only technique able to directly investigate the functional role of white matter tracts in humans. In addition, combining serial perioperative functional neuroimaging and online intraoperative DES enables the study of mechanisms underlying cerebral plasticity. Therefore, DES led our group to elaborate new individual and integrative models of language. These networking models have resulted in a better knowledge of the dynamic spatiotemporal reorganization of parallel and interactive circuits in adults, and a better knowledge of the limitations of neuroplasticity, mainly represented by the connectome. Understanding axonal connectivity is crucial to optimizing neurolinguistic models, which should integrate the anatomic constraints represented by subcortical pathways. Finally, it is worth noting that this improved knowledge of language networks is a prerequisite for restoring brain functions in aphasic patients, in particular by opening new approaches in the field of brain-computer interfaces (Mandonnet & Duffau, 2014).

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CHAPTER 9

DIFFUSION IMAGING METHODS IN LANGUAGE SCIENCES

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INTRODUCTION

OVER the last two centuries, neuronal correlates of language have been investigated employing various structural and functional methods. Structural methods include traditional post-mortem dissections (Broca, 1865; Wernicke, 1874), computer tomography (Naeser & Hayward, 1978; Yarnell, Monroe, & Sobel, 1976) and magnetic resonance imaging (MRI) to visualize damage to cortical and subcortical anatomy (DeWitt, Grek, Buonanno, Levine, & Kistler, 1985; see Wilson, Chapter 2 in this volume). Functional methods include electro- and magneto-encephalography (Friederici, von Cramon, & Kotz, 1999; Hari & Lounasmaa, 1989; Salmelin, 2007; Tikofsky, Kooi, & Thomas, 1960; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume), functional MRI (McCarthy, Blamire, Rothman, Gruetter, & Shulman, 1993; see Heim & Specht, Chapter 4 in this volume), direct electrical stimulation (see Duffau, Chapter 8 in this volume), and tomography methods for brain hemodynamics and metabolism, such as single photon emission computerized tomography (Perani, Vallar, Cappa, Messa, & Fazio, 1987) and positron emission tomography (Cappa et al., 1997; Wise, Hadar, Howard, & Patterson, 1991). These methods, albeit complementary to each other in terms of spatial and temporal resolution, are insufficient to investigate the structural connections supporting distributed language processing in the human brain. Additionally, they are unable to provide quantitative measures of tract anatomy to study, for example, structural asymmetry between the two hemispheres in the same subject or across groups.

Understanding the anatomy of language networks and its variability in both the healthy population and patients represents one of the most significant contributions of diffusion tractography to modern neurolinguistics. First, by looking at tracts we can reconcile data on patients who present with aphasia and "atypical" lesion location (Catani et al., 2012a). These patients often have lesions that are distant from regions dedicated to specific language functions. The classical example is represented by patients presenting with Broca's aphasia with retro-rolandic lesions sparing Broca's area but affecting tracts connected to this area (Basso, Lecours, Moraschini, & Vanier, 1985; Catani et al., 2012a). Second, and most important, a network approach emphasizes the parallel and integrated nature of the cognitive processes underlying language. This network approach is a fundamental evolution away from static and rigid localizationist models of brain function and helps to broaden the disconnectionist approach to a wider range of language disorders in neurology and psychiatry (Catani & ffytche, 2005).

In the last 15 years, diffusion tractography has become an established noninvasive quantitative method to study connectional anatomy in the living human brain. When applied to language, tractography has proven to be a powerful tool to gain new insights into the functional anatomy of language. For example, tractography has indicated that networks for language and social communication are more complex than previously anticipated (Catani & Bambini, 2014; Catani, Jones, & ffytche, 2005; Turken & Dronkers, 2011) and extend to areas and connections that were not included in the classical Broca-Wernicke-Geschwind model (Geschwind, 1965). This complexity is heterogeneous among the healthy population, with striking differences between the male and the female brain (Catani et al., 2007) and across ages (Budisavljevic et al., 2015; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). These inter-individual differences are beginning to explain the observed variance in language performances among healthy controls (Catani et al., 2007; Lopez-Barroso et al., 2013) and in the recovery of language after stroke (Forkel et al., 2014).

In this chapter, we will discuss the principles of diffusion imaging and tractography alongside examples of how this method has informed our understanding of language development, variance in language performances, and language disorders.

PRINCIPLES OF DIFFUSION TRACTOGRAPHY

The history of diffusion imaging and tractography spans about 30 years and can be broadly split into two halves. The first 15 years extend from 1985, the year that the first diffusion-weighted images of the brain were acquired, to 1999, when a handful of researchers proposed diffusion tractography as a method to study trajectories of white matter pathways in the living brain (Le Bihan et al., 1986; Conturo et al., 1999; Jones, Simmons, Williams, & Horsfield, 1999; Mori, Crain, Chacko, & van Zijl, 1999). The second half (i.e., 2000–2015) has been characterized by a systematic application of diffusion methods, including tractography, to study the anatomy of connections in the healthy population and the impact of disorders on white matter organization in patient cohorts. While novel methods for diffusion imaging are continuously proposed, here we focus on current mainstream methods that are widely employed.

Diffusion Weighted Imaging

Diffusion weighted imaging (DWI) is a noninvasive, in vivo MRI technique that quantifies water diffusion in biological tissues. In neuronal tissue, the displacement of water molecules is not random due to the presence of biological structures such as cell membranes, filaments, and nuclei. These structures hinder water diffusion in the three-dimensional space. In the white matter, the overall displacement is reduced unevenly due to the presence of axonal membranes and myelin sheets, which hinder water diffusion in a direction perpendicular to the axonal fibers. Within a single voxel, water diffusion can be described geometrically as an ellipsoid (the tensor) calculated from the diffusion coefficient values (eigenvalues, λ_{1-3}) and orientations (eigenvectors, ν_{1-3}) of its three principal axes (Figure 9.1) (Basser, Mattiello & Le Bihan, 1994). A detailed analysis of the tensor can provide precise information about not only the average water molecular displacement within a voxel (e.g., mean diffusivity), but also the degree of tissue anisotropy (e.g., fractional anisotropy), and the main orientation of the underlying white matter pathways (e.g., principal eigenvector or color-coded maps). These indices provide complementary information about the microstructural composition and architecture of brain tissue.

Mean diffusivity (MD) is a rotational invariant quantitative index that describes the average mobility of water molecules and is calculated from the three eigenvalues of the tensor according to the formula $MD = [(\lambda 1 + \lambda 2 + \lambda 3)/3]$. Voxels containing gray and white matter tissue show similar MD values (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). MD reduces with age within the first years of life and increases in those disorders characterized by demyelination, axonal injury, and edema (Beaulieu, 2009).

The fractional anisotropy (FA) index ranges from 0 to 1 and represents a quantitative measure of the degree of anisotropy in biological tissue (Figure 9.1). In the healthy adult brain, FA varies typically between 0.2 (e.g., in gray matter) and ≥0.8 in some white matter regions with highly myelinated parallel fibers. In the white matter FA provides information about the local organization of the fibers (e.g., parallel, crossing, kissing fibers) and their biological features (e.g., degree of myelination, axonal membrane permeability, etc.). FA changes in pathological tissue (e.g., demyelination, edema, ischemia) and is therefore commonly used as an indirect index of microstructural disorganization or integrity in brain disorders.

Perpendicular $[(\lambda 2 + \lambda 3)/2]$ and parallel diffusivity ($\lambda 1$) describe the diffusivity along the principal directions of the water diffusion. The perpendicular diffusivity, also indicated by the term radial diffusivity (RD), is generally considered a more sensitive index of axonal or myelin damage, although interpretation of their changes in regions with crossing fibers is not always straightforward (Dell'Acqua & Catani, 2012). The principal eigenvector and the red-green-blue (RGB) color-coded maps are particularly useful to visualize the principal orientation of the tensor within each voxel (Pajevic & Pierpaoli, 1999; see Figure 9.1).

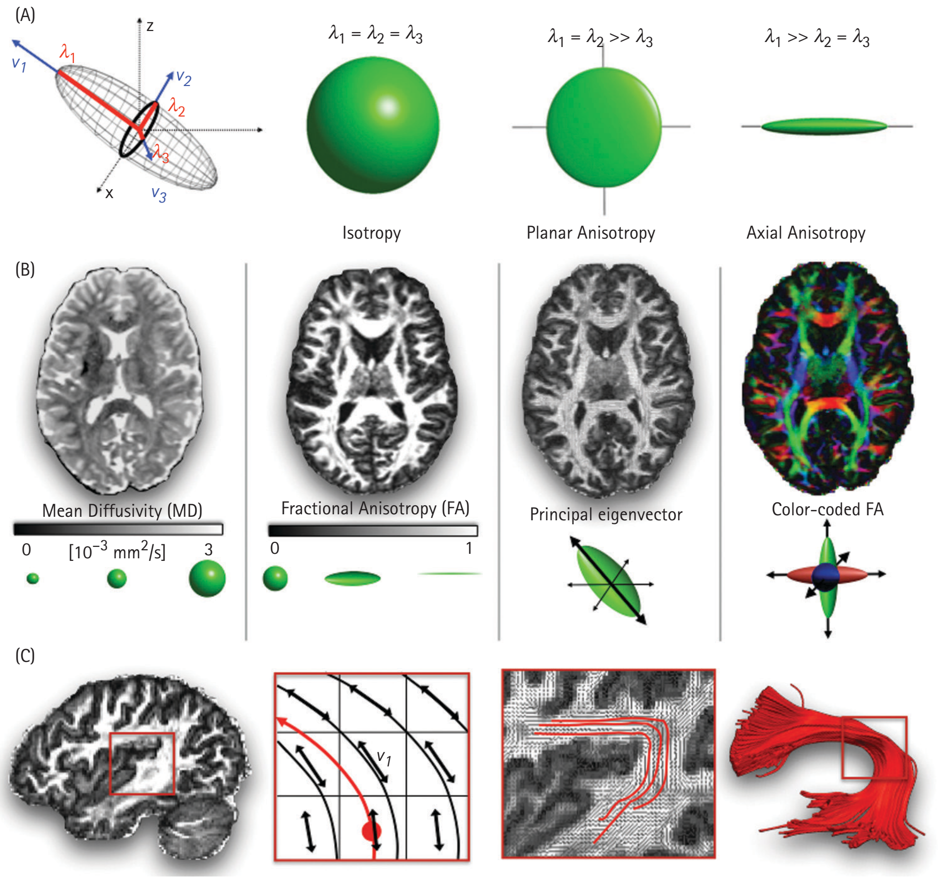
(A)
z
x
v1
λ1
v2
λ2
λ3
v3
λ1 = λ2 = λ3
λ1 = λ2 >> λ3
λ1 >> λ2 = λ3
Isotropy
Planar Anisotropy
Axial Anisotropy
(B)
Mean Diffusivity (MD)
0
[10-3 mm2/s]
3
Fractional Anisotropy (FA)
0
1
Principal eigenvector
Color-coded FA
(C)
v1

FIGURE 9.1. Principles of diffusion tensor imaging (DTI) tractography. (A) Visualization of the diffusion tensor as an ellipsoid. The size and the shape of the tensor are defined by the three eigenvalues (λ1, λ2, λ3 in red), while the spatial orientation is described by the three eigenvectors (v1, v2, v3 in blue). In biological tissues, the tensor can vary between three possible configurations: (1) isotropy or weak anisotropy (equal or similar diffusivity along the three eigenvalues) is commonly observed, for example, inside the ventricles (isotropy) or in the gray matter (weak anisotropy); (2) planar anisotropy (unequal diffusivity between of one eigenvalue and the other two) is common in voxels containing, for example, two groups of crossing or diverging fibers; and (3) axial anisotropy is typical of voxels containing parallel fibers (unequal diffusivity between the axial eigenvalue and the two perpendicular eigenvalues). (B) Exemplified indices extracted from diffusion data, such as mean diffusivity (MD), fractional anisotropy (FA), principle eigenvector, and color-coded FA maps. (C) Streamline tractography is based on the assumption that in each white matter voxel the principal eigenvector (black arrows) is tangent to the main trajectory of the underlying fibers (black lines). Starting from a region of interest (red circle), the tractography algorithm propagates, voxel by voxel, a streamline (red) by piecing together neighboring principal eigenvectors. An example is shown in the neighboring panel where the streamlines are tracked on a principal eigenvector map and the tractography reconstruction of the arcuate fasciculus is visualized as 3D streamtubes.

Tractography-Based Reconstruction of White Matter Pathways

Compared to previously established methods used for studying tract anatomy, such as axonal tracing in animals or human post-mortem blunt dissection, diffusion tensor tractography offers the unique advantage of being a completely noninvasive technique, and therefore its use is not restricted to nonhuman primates but can be applied to the living human brain. Furthermore, the data required to obtain tract reconstructions with tractography can be readily acquired on standard clinical MRI systems with scanning times typically ranging between 5 and 20 minutes. Recently, methodological advances have enabled shorter acquisition times, which makes tractography a suitable tool for clinical populations, including children with developmental language disorders (Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010) and adults with stroke (Forkel et al., 2014) or neurodegenerative disorders (Catani et al., 2013; D'Anna et al., 2016).

The main assumption underpinning diffusion tensor tractography is that the diffusion of water molecules can be described mathematically by a diffusion tensor whose principal axis aligns with the predominant orientation of the fibers contained within each voxel (Basser, Mattiello, & Le Bihan, 1994). Based on this assumption, tractography algorithms track white matter trajectories by inferring axonal continuity from voxel to voxel (Figure 9.1). In simple terms, this process is achieved by following the direction of maximum diffusion from a given voxel into a neighboring voxel (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Poupon et al., 2000). How to piece together discrete estimates of water diffusion between contiguous voxels depends on the algorithm used and the choice of some tracking and stopping parameters. Most tractography algorithms adopt angular and FA thresholds to avoid unrealistic fiber bending or tracking outside of white matter regions.

Diffusion tractography can be used to generate indirect measures of tract volume and microstructural properties of fibers. Common measures of tract volume are the overall number of streamlines that compose a single tract, or the total volume of voxels intersected by a tract (Dell'Acqua & Catani, 2012). Tractography-derived interhemispheric differences in tract volume are widely reported in the literature, especially for language pathways (Catani et al., 2007), although their exact interpretation is not straightforward. Histological properties that are likely to determine larger tract volumes include axonal diameter and myelination of fibers, high axonal density and fiber dispersion, and the presence of fiber crossing and branching.

In addition to tract volume, for each voxel intersected by streamlines, other diffusion indices can be extracted and the total average can be extrapolated. Examples include the fractional anisotropy, mean diffusivity, and parallel and radial diffusivity. These can provide important information on the microstructural properties of fibers and their organization. Asymmetry in fractional anisotropy, for example, could indicate differences in the axonal anatomy (intraxonal composition, axon diameter, and membrane permeability), fiber myelination (myelin density, internodal distance, and myelin distribution), or fiber arrangement and morphology (axonal dispersion, axonal crossing, and axonal branching) (Beaulieu, 2002; Concha, 2014). Other diffusion measurements may reveal more specific fiber properties. Changes in axial diffusivity measurements, for example, could be related to intraxonal composition, while radial diffusivity may be more sensitive to changes in membrane permeability and myelin density (Song et al., 2002). These in vivo diffusion-based measurements allow connectional anatomy to be defined at different scales from microstructure to gross anatomy for individual tracts and across the lifespan.

TRACTOGRAPHY-BASED MODELS OF LANGUAGE NETWORKS

In the past 15 years, tractography has greatly contributed to contemporary revisions of anatomical models of language networks. New pathways, which were not previously described in animal models, have been identified and their anatomy characterized in the human brain by tractography (Figure 9.2) (Catani et al., 2005; Catani et al., 2012; Lawes et al., 2008).

In general, tractography has identified two sets of white matter connections for language and social communication: a *core network* encompassing classical perisylvian language regions, and an *extended network* connecting perisylvian regions to other cortical and subcortical hubs (Catani & Bambini, 2014; Catani & Mesulam, 2008). The paragraphs that follow do not represent a comprehensive account of the literature on the tracts forming the core and extended language networks, but are intended to provide examples of how tractography has been used to address specific questions in healthy cohorts and in patients with language disorders.

The Core Language Network

The *arcuate fasciculus* is a dorsal perisylvian tract connecting Wernicke's region in the posterior temporal lobe to Broca's region in the inferior frontal lobe (Figure 9.2 A). Early tractography studies showed that the classical Wernicke-Broca-Geschwind model was an oversimplification of the real anatomy (Catani et al., 2005, Figure 9.2 B). Indeed, two parallel pathways within the arcuate fasciculus have been identified: the medial, direct pathway connecting Wernicke's region with Broca's region (i.e., the arcuate fasciculus *sensu strictu* or long segment), and the indirect pathway consisting of an anterior segment linking Broca's region to Geschwind's region (encompassing the angular and supramarginal gyrus in the inferior parietal lobe) and a posterior segment between Geschwind's region and Wernicke's region. There is evidence that this anatomical division has important functional implications (Catani & Mesulam, 2008).

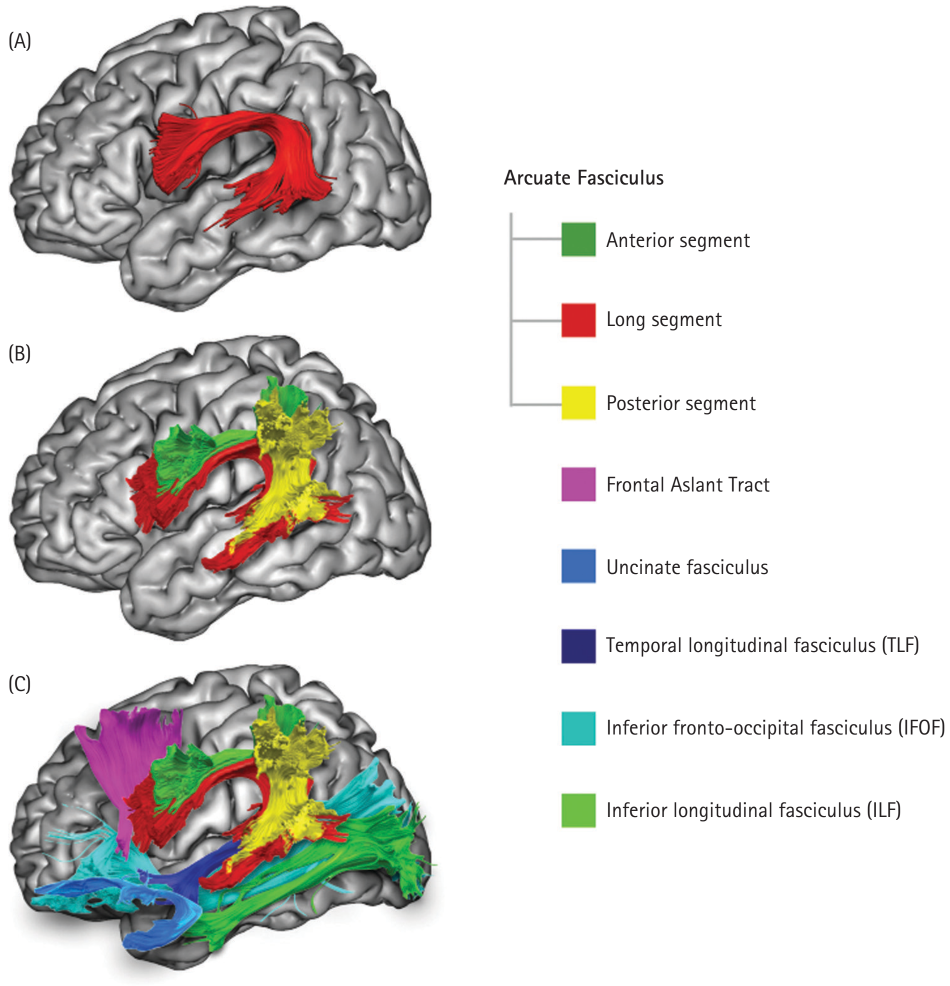
(A)
(B)
(C)
Arcuate Fasciculus
Anterior segment
Long segment
Posterior segment
Frontal Aslant Tract
Uncinate fasciculus
Temporal longitudinal fasciculus (TLF)
Inferior fronto-occipital fasciculus (IFOF)
Inferior longitudinal fasciculus (ILF)

FIGURE 9.2. Tractography-based reconstruction of the language networks from classical models to contemporary neurolinguistics. (A) Classical language model with the arcuate fasciculus connecting Broca's region in the inferior frontal gyrus to Wernicke's region in the superior temporal gyrus. (B) Extension of the classical arcuate fasciculus *sense strictu* to include the anterior segment, connecting inferior frontal to inferior parietal lobe, and the posterior segment linking the inferior parietal to the temporal lobe. (C) Current model of an extended language network beyond the three segments of the arcuate fasciculus. The frontal aslant tract (FAT) connects the inferior frontal gyrus to the pre-supplementary motor cortex. The ventral network includes the uncinate fasciculus between the anterior temporal lobe and the orbital frontal and inferior frontal cortex, the temporal longitudinal fasciculus (TLF) between the posterior temporal lobe and the temporal pole, the inferior fronto-occipital fasciculus (IFOF) connecting the ventral frontal cortex to the occipital cortex, and the inferior longitudinal fasciculus (ILF) between the occipital and anterior temporal cortex.

Lopez-Barroso et al. (2013) demonstrated that performance in word learning correlates with microstructural properties (as measured with DTI) and strength of functional connectivity (as measured with fMRI) of the left direct segment. In addition, the long segment tends to myelinate later in childhood, and its maturation is associated with the acquisition of syntactic abilities (Brauer, Anwander, Perani, & Friederici, 2013). These studies indicate that our ability to learn new words and develop syntax relies on an efficient and fast communication between auditory temporal and motor frontal regions. The presence of a less prominent long segment in nonhuman primates might explain human linguistic specialization based on an exceptional auditory memory unique to our species (López-Barroso et al., 2013; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012).

While the direct pathway may support auditory-motor integration, which is crucial during early stages of language acquisition, the role of the indirect pathway and Geschwind's region could be more complex and related to linking semantic and phonological processes (Newhart et al., 2012) for tasks that require verbal working memory to understand complex sentences (Jacquemot & Scott, 2006). In addition, the temporoparietal regions connected by the posterior segment activate in tasks for the comprehension of ambiguous sentences (e.g., garden-path paradigms) (den Ouden, Walsh Dickey, Anderson, & Christianson, 2016), metaphors (Bambini, Gentili, Ricciardi, Bertinetto, & Pietrini, 2011), and indirect speech acts (Bašnáková, Weber, Petersson, van Berkum, & Hagoort, 2014), as well as for tasks that involve the representation of discourse and the protagonist's perspective in narratives (Mason & Just, 2009). A recent model for social communication and language evolution and development (SCALED) suggests that the posterior network supports complex integration and inferential mechanisms that reach several layers of meta-representations for the attribution of beliefs and emotional states to conversational partners (Catani & Bambini, 2014).

Among all tracts of the human brain, the arcuate fasciculus displays the greatest degree of inter-hemispheric and inter-individual asymmetry. By extracting volumetric measurements of the three segments of the arcuate fasciculus, it has been demonstrated that the long segment is strongly left lateralized in 60% of the population, whereas the remaining 40% show a bilateral pattern. The bilateral pattern seems to be more prevalent among the female population as compared to males. In the extremely left lateralized group, males represent 68% while females account for 32%, in contrast to the bilateral group with 80% females but only 20% males. Moreover, the pattern of asymmetry correlated with performances on the California Verbal Learning Test (CVLT), a verbal memory task that relies on semantic clustering for word learning and retrieval; the correlation indicated that a more bilateral representation was advantageous for the retrieval of word lists (Catani et al., 2007).

A better understanding of the pattern of asymmetry of the long segment has important implications. First, it offers a neuroanatomical explanation for the observed performances of females over males on verbal learning tasks (Kramer, Delis, & Daniel, 1988). Second, the high variability of asymmetry in the general population can help to identify different trajectories to language recovery in patients with aphasia after left hemisphere stroke. This was demonstrated employing tractography in a longitudinal study of aphasia recovery in which the volumetric measurements of the long segment in the right hemisphere were predictive of aphasia recovery six months after stroke (Forkel et al., 2014). Tractography measurements of the volume of the right long segment improved the predictive value for recovery above and beyond models accounting for demographics alone by explaining an additional 30% of the observed variance in recovery at six-months post stroke (Forkel et al., 2014).

The Extended Language Network

The extended language network is composed of several tracts, including the uncinate fasciculus, the frontal aslant tract, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the temporal longitudinal fasciculus and the fronto-insular tracts (Figure 9.2 C).

The *uncinate fasciculus*, which connects the anterior temporal lobe to the orbitofrontal region and part of the inferior frontal gyrus (Catani, Howard, Pajevic, & Jones, 2002), is classically considered to be a major pathway of the limbic system (Catani, Dell'Acqua, & Thiebaut de Schotten, 2013). In addition to its role in emotion processing and behavior, the uncinate fasciculus has been associated with tasks involving lexical retrieval, semantic association, and naming (Heide, Skipper, Klobusicky, & Olson, 2013). The uncinate fasciculus is severely damaged in patients with the semantic variant of primary progressive aphasia, and the severity of its degeneration correlates with scores on tests for naming (Catani et al., 2013).

The *frontal aslant tract* is a recently described pathway connecting Broca's region with dorsal medial frontal areas, including the pre-supplementary motor area and cingulate cortex (Catani et al., 2012; Ford, McGregor, Case, Crosson, & White, 2010; Lawes et al., 2008). Medial regions of the frontal lobe facilitate speech initiation through direct connection to the precentral gyrus and the pars opercularis and triangularis of the inferior frontal gyrus. Patients with lesions to these areas present with various degrees of speech impairment, from a total inability to initiate speech (i.e., mutism) to mildly altered fluency. Tractography studies have demonstrated damage to the frontal aslant tract in patients with the nonfluent/agrammatic form of primary progressive aphasia (Catani et al., 2013; Mandelli et al., 2014).

The inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus convey visual inputs to the frontal and anterior temporal lobe, respectively. The proposal of a prominent role of these two tracts in semantic cognition has been originally suggested by intraoperative stimulation studies reporting the observation of anomia for stimulation of the white matter fibers running within the external/extreme capsule or the anterior temporal regions (see Duffau, Chapter 8 in this volume). This proposal is challenged by the prominent role of the anterior temporal cortex in semantic cognition as demonstrated in patients with the semantic variant of primary progressive aphasia (Catani et al., 2013) and the lack of cases of anomic deficits in patients with stimulation of the most posterior portion of the inferior fronto-occipital fasciculus and inferior longitudinal fasciculus. Also the inability of determining the exact fiber localization during intraoperative stimulation raises the question of whether other tracts running in parallel with the inferior fronto-occipital fasciculus or the inferior longitudinal fasciculus have been stimulated instead. Among these tracts the recently described temporal longitudinal fasciculus connecting Wernicke's region to the anterior temporal pole is likely to be involved in single word comprehension and retrieval (Maffei et al., 2017).

The frontal operculum is connected to the insula through a system of short U-shaped *fronto-insular tracts* (Catani et al., 2012). Direct insular inputs to Broca's region from the insula provide visceral and emotional information for speech output modulation according to internal states. Lesions to these insular connections may result in motor aprosodia (e.g., flat intonation) in the right hemisphere (Witteman et al., 2014), while in the left hemisphere it may be associated with apraxia of speech (Dronkers, 1996).

Limitations and Future Directions

The advent of diffusion tractography signified a fundamental advancement of our understanding of networks underpinning language functions. The ability to track connections in the living human brain offers the possibility to move beyond network models based on axonal tracing in monkeys and perform direct clinical-anatomical correlations in the living human brain. Despite the obvious advantages, tractography has several limitations, some of which will be briefly discussed in the following.

Compared to classical axonal tracing studies, tractography is unable to differentiate anterograde and retrograde connections, detect the presence of synapses, or determine whether a pathway is functional. In addition, while injected tracers follow the termination of single axons, tractography follows the principal axis of the water diffusion, which is obtained by averaging the MRI signal within a voxel. Typically, the voxel resolution is too low to identify small fiber bundles. The level of noise in the diffusion data and the intrinsic MRI artifacts constitute important factors that affect the precision and accuracy of the diffusion measurements and, as a consequence, the quality of the tractography reconstruction (Basser et al., 2000; Le Bihan et al., 2006). Finally, diffusion tensor tractography assumes that fibers in each voxel are well described by a single orientation estimate, which is a valid assumption for voxels containing only one population of fibers with a similar orientation. The majority of white matter voxels, however, contain populations of fibers with multiple orientations; in these regions fibers cross, kiss, merge, or diverge, and the tensor model is inadequate to capture this anatomical complexity (Basser et al., 2000). More recent tractography developments based on HARDI (high angular resolution diffusion imaging) methods (Dell'Acqua et al, 2010; Dell'Acqua & Tournier, 2018; Frank, 2001) and appropriate processing techniques are able to partially resolve fiber crossings (Tournier, Calamante, Gadian, & Connelly, 2004; Tuch, 2004; Wedeen et al., 2005; Alexander, 2005; Behrens et al., 2007). Among the HARDI methods, spherical deconvolution algorithms (Figure 9.3) have been used to reconstruct white matter

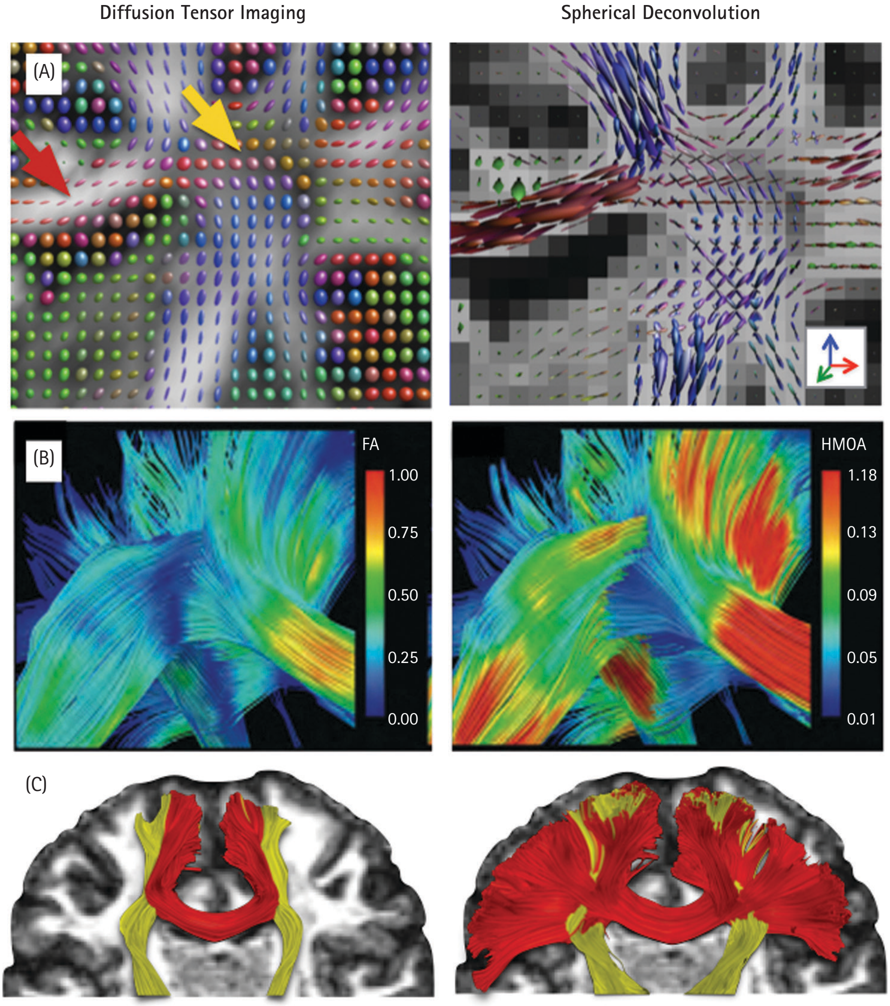

FIGURE 9.3. Comparison of diffusion tensor imaging (DTI) and advanced diffusion tractography based on spherical deconvolution. (A) Visualization of voxel-wise fibre orientation in a coronal slice passing through the corpus callosum using diffusion tensor imaging (left) and spherical deconvolution (right). The shape and orientation of the tensor model indicates the average diffusion properties and orientation of all fibre populations contained within a voxel. The spherical deconvolution model differentiates between different fiber populations within each voxel and gives fiber specific information . (B) Eigenvector map visualization of the white matter organization of the corpus callosum and the corona radiata based on the tensor model (left) and on spherical deconvolution (right). The arcuate fasciculus and the lateral projections of the corpus callosum are distinct tracts that cross at the level of the corona radiata where their fibers occupy the same voxels. Fractional anisotropy values extracted for each voxel that contain crossing fibers indicate low values for both tracts. The low FA values are due to the weak anisotropic properties of the voxels containing crossing fibers. Spherical deconvolution permits to calculate the hindrance modulated orientational anisotropy (HMOA) index, which is a measure of tissue anisotropy specific of each fiber population occupying a voxel. In this example the fibers of the arcuate fasciculus and corpus callosum that cross at the level of the corona radiata show different HMOA values even when they occupy the same voxel. (C) Virtual dissections of the corpus callosum (red) and corticospinal tracts (yellow) based on diffusion tensor tractography (left) and spherical convolution (right). The diffusion tensor reconstruction of the corpus callosum is limited only to its most central part while tractography based on spherical deconvolution (right) shows streamlines of the corpus callosum that cross the corticospinal tracts and reach the lateral cortex.

pathways in regions with multiple fiber orientations, such as in the triangle between the corpus callosum, the superior longitudinal fasciculus, and the cortico-spinal tract (Thiebaut de Schotten et al., 2011; Dell'Acqua, Simmons, Williams, & Catani, 2013).

All these limitations may lead to tracking pathways that do not exist (false positive) or fail to track those that do exist (false negative). A few studies have so far dealt with the issue of validating the tractography results with neuronal tracers (Dauguet et al., 2007; Dyrby et al., 2007) or performing reproducibility analysis on human subjects using post-mortem blunt dissections or diffusion data sets acquired at high spatial resolution (Heiervang et al., 2006; Lawes et al., 2008; Wakana et al., 2007; Catani et al., 2012b).

It is evident from all the considerations in the preceding that interpretation of tractography results requires experience and a priori anatomical knowledge. This is particularly true in the diseased brain, where alteration and anatomic distortion due to the presence of pathology, such as brain edema, hemorrhage, and compression, generates tissue changes likely to lead to a greater number of artifactual reconstructions (Catani, 2006; Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008; Dell'Acqua & Catani, 2012).

The recent development of MRI scanners with stronger gradients and multi-band acquisition sequences represents one of many steps toward a significant amelioration of the diffusion tractography approach. The possibility of combining tractography with other imaging modalities or direct electrical stimulation methods will contribute to a more complete picture of the functional anatomy of human language pathways.

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PART II

DEVELOPMENT AND PLASTICITY

CHAPTER 10

NEUROPLASTICITY

Language and Emotional Development in Children with Perinatal Stroke

JUDY S. REILLY AND LARA R. POLSE

The term "plasticity" derives from the ancient Greek *plasso* (*platho* in modern Greek, *πλάϑω*) and is often employed in reference to brain adaptation and reorganization in response to a cerebral injury. Plasticity in reference to the nervous system first appeared when William James (1890) proposed that the human brain has the capacity to change and reorganize, noting that "[o]rganic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity." In the early twentieth century, Ramon y Cajal (1904) extended this notion by suggesting that new behavioral learning was supported by neuronal change and development. Such statements suggest that plasticity is not only a response to insult, but rather that plasticity is characteristic of, and functions as, the neural mechanism supporting learning and development throughout the life span (Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Stiles, Reilly, Levine, Trauner, & Nass, 2012). In the young child, as tissue is presumably less specified and neurons less committed to specific functions, neuroplasticity has a wider potential in the developing brain than in an adult brain that has already committed neural resources to various cognitive functions. Children who have suffered a unilateral focal lesion before their first month of postnatal life represent an extraordinary case in which the brain must adapt and (re)organize in the face of this early lesion. As such, the development of these children with perinatal stroke (PS) provides a unique context to elucidate the nature, extent, and limits of neuroplasticity.

When we began our studies on children with PS about 30 years ago, we looked to the adult model as a means to understand brain organization for language, as the adult model represents the steady or end state of development. As the majority of chapters in this volume attest, we currently know a great deal concerning the neural substrates that participate in language processing in adults (e.g., see, in this volume, Peelle, Chapter 12; Rapp & Purcell, Chapter 17; de Zubicaray & Piai, Chapter 19; Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24; Bornkessel-Schlesewsky & Schlesewsky, Chapter 27; Catani, Jones, & ffytche, 2005; Price, 2010; Vigneau et al., 2006). An extensive literature of imaging and neuropsychological studies on neurotypical and stroke patients over the last 30 years has broadly confirmed and refined the original findings of Broca and Wernicke: that there exists a predominantly left hemisphere fronto-temporal neural network for language processing. In contrast to this broad and extensive literature on the organization of language in the adult brain, we are just beginning to understand how the developing brain achieves this mature state. An early comment from Jules Cotard, a colleague of Broca, suggested that strokes early in development do not have the same consequences as later strokes: "Intelligence may be normal when a hemisphere is destroyed during infancy . . . in these cases one never encounters aphasia" (translated and quoted in Pearn & Gardner-Thorpe, 2002, p. 1401). Almost a century later, Basser (1962) and Lenneberg (1967) presented empirical evidence in support of this notion, leading Lenneberg to hypothesize that the two hemispheres of the brain were initially equipotential for language. More than twenty-five years of prospective studies chronicling the linguistic development of children with PS (Bates & Roe, 2001; Bates et al., 1997; Feldman, 1994; Feldman, Holland, Kemp, & Janosky, 1992; Reilly, Bates, & Marchman, 1998; Reilly, Levine, Nass, & Stiles, 2008; Reilly, Losh, Bellugi, & Wulfeck, 2004; Reilly, Wasserman, & Appelbaum, 2013; Rowe, Levine, Fisher, & Goldin-Meadow, 2009; Stiles, Reilly, Levine, Trauner, & Nass, 2012; Thal et al., 1991; Thal, Reilly, Seibert, Jeffries, & Fenson, 2004) have demonstrated that, unlike adults with homologous stroke, children exhibit remarkable progress in language acquisition after PS. In contrast, the developmental trajectories for other cognitive systems (e.g., spatial cognition and affective expression) in these same children have shown subtle, but persistent deficits reminiscent of adults with late-onset strokes (Stiles et al., 2012). In this chapter, we present findings on language development in children who sustained a pre- or perinatal unilateral stroke, and to complement these studies, we also look at the development of another communicative system, affective expression, in these same children, as it reflects a rather different developmental trajectory. These prospective studies of this rare group of children (1/4,000 live births; Lynch & Nelson, 2001) provide a unique window into the development of the neural substrates for language and affect. Specifically, they afford a context to investigate the degree to which particular brain regions may be privileged for specific behavioral functions, as well as how the developing brain adapts to organize alternative pathways in the wake of an early insult.

The fields of linguistics and affective science both have long, but rather independent histories (see van Berkum, Chapter 29 in this volume). However, in our view, the development of affective expression provides an intriguing and informative complement to language. As adult speakers, we consider language to be our primary communicative system; however, each utterance is produced and interpreted in an emotional context. We can color or modulate our spoken utterances lexically, as well as with prosody and facial expression. As such, for adults, the two expressive systems are smoothly integrated, and their co-expression constitutes the expressed message. In children, however, affective communication significantly predates the onset of productive language. Neonates orient and attend to faces (or face-like stimuli; Grossman & Johnson, 2007; Johnson & Morton, 1991); moreover, newborns can and do produce a broad range of emotional facial behaviors (Oster, 1978). First social smiles appear at about 4–6 weeks of age, when children also recognize their familiars by facial features alone (de Shonen & Mathivet, 1989); babies are smiling frequently at their family members by three months and are using a smile or a cry instrumentally to engage or summon others by 3–4 months of age. By the infant's first birthday, when first words typically emerge, the child is already a competent affective communicator, employing facial expression, gestures, and affective utterances not only when interpreting the communications of others, but also to communicate her own interests and desires. Interestingly, whereas the perisylvian regions of the left hemisphere are most implicated in language processing, when we look to the neural substrates of affective processing in adults, it is those with late-onset right hemisphere lesions who show flattened affect both facially and vocally (e.g., Blonder, Bowers, & Heilman, 1991; Blonder, Burns, Bowers, Moore, & Heilman, 1993; Blonder et al., 2005; Borod, 2000; Borod, Bloom, Brickman, Nakhutina, & Curko, 2002; Pell, 2006). Given the developmental precocity of emotional signaling, and the differential adult neural profiles for emotion and language, investigating emotional expression in children with PS provides a counterpoint to their language development and offers a more comprehensive understanding of neuroplasticity.

The chapter is organized in the following manner: we begin with a description of the children with PS; we then turn to the adult model of brain-language and brain-emotion relations to provide a backdrop for our developmental studies; the adult profiles can be considered an end or steady state of development. We go on to document language development in children with PS from first babbling in infancy to recounting personal narratives in adolescence. We then look at the development of emotional expression in these children to refine and contextualize our understanding of the extent and nature of neuroplasticity. Finally, we consider how the developing neural substrates for language and emotion in neuro-typical children play a role in the extent of plasticity observed following a stroke.

CHILDREN WITH PERINATAL STROKE

Perinatal stroke is a rare occurrence; the incidence is about 1 in 4,000 live births (Lynch, Hirtz, DeVeber, & Nelson, 2002; Lynch & Nelson, 2001). These children have a documented unilateral lesion of acute onset, the result of a stroke (infarct or hemorrhage), which occurred sometime in the last trimester of gestation up until 28 days postnatally with no history of more global damage (e.g., bacterial meningitis, encephalitis, or severe closed head trauma). Their lesions have been documented by computed tomography (CT) or magnetic resonance imaging (MRI), and tend to be in the left, rather than the right, hemisphere. The children in our study group have normal or corrected auditory and visual acuity, and they are of English-speaking background. Their very early cerebrovascular events provide a unique opportunity to investigate neuroplasticity for language and other cognitive systems. The children also offer an informative comparison group to the well-studied population of adults with late-onset unilateral strokes, as the differences in cognitive/behavioral profiles between these groups can be attributed to the development and the plasticity of the developing brain.

THE NEURAL UNDERPINNINGS OF LANGUAGE: ADULTS

Adults with unilateral late-onset stroke have been studied for well over a century, with the aim of identifying regions of the brain that are associated with specific functional language processes (see, in this volume, Blumstein, Chapter 1, and Wilson, Chapter 2). In 1861, Broca described a patient with damage to the left inferior frontal gyrus (Broca's area) who exhibited severely impaired expressive language, ostensibly without a comprehension deficit. Shortly thereafter, it was observed that patients with damage to the posterior temporal lobe (Wernicke's area) had significant deficits in comprehension yet apparently fluent productive grammar (Goodglass, 1993). From these observations came the Wernicke-Lichtheim model of language (Lichtheim, 1885; Wernicke, 1874), in which it was proposed that auditory word comprehension occurs in the left posterior temporal region, and motor word representations (for word production) are localized in the left inferior frontal regions of the brain. Structural and functional neuroimaging research has contributed to a greater understanding of the complexities underlying these elegant models of language (see Price, 2010, for a review), yet the basic tenets of the early models are broadly substantiated in current neuroimaging and patient research. Specifically, language networks in the anterior left hemisphere (particularly inferior frontal gyrus) tend to be preferentially involved in language production and semantic processing; regions in the left hemisphere superior temporal lobe tend to be involved in the comprehension of formal aspects of language, such as grammar and syntax.

While it was previously believed that the right hemisphere was uninvolved or only marginally involved in processing language, it is now clear that the right hemisphere plays an important (albeit qualitatively distinct) role (Joanette & Brownell, 1993; Joanette, Goulet, & Hannequin, 1990; Jung-Beeman, 2005; Kaplan, Brownell, Jacobs, & Gardner, 1990). It is vital for discourse processing, cohesion, pragmatic language (Borod et al., 2000), and nonliteral language such as metaphors, idioms, and sarcasm (Bottini et al., 1994; see Rapp, Chapter 28 in this volume), as well as affective communication (e.g., Borod, Bloom, Brickman, Nakhutina, & Curko, 2002; see van Berkum, Chapter 29 in this volume). With this brief overview of brain-language relations in adults, we now consider the adult profile for emotional expression.

The Neural Underpinnings of Affect: Adults

In adults with late-onset right hemisphere lesions, identity and recognition of emotional facial expression and affective prosody are negatively impacted. Both clinical reports and experimental studies document affective deficits for both facial and vocal channels in those with right hemisphere stroke as compared to those with left hemisphere stroke and neurotypical controls (e.g., Blonder et al., 2005; Borod, 2000; Borod, Koff, Lorch, & Nicholas, 1985; Ross, 1981). Haxby and colleagues (Haxby, Hoffman, & Gobbini, 2000, 2002) have proposed a "core" face network for the recognition of faces, as well as an "extended" network to extract meaningful information (e.g., emotion) from that face. The core network includes the fusiform gyrus, occipital gyri, and the superior temporal sulcus bilaterally; for emotion processing, the extended network also includes limbic areas, including amygdala and insula (see also Fusar-Poli et al., 2009).

Drawing from both behavioral and imaging studies from neurotypical adults and stroke patients, Adolphs (2002) proposed a model for the perception of emotional facial expression that recruits the right visual cortices, especially occipital gyrus, right fusiform gyrus, and superior temporal gyrus, insula and amygdala, orbitofrontal cortex (R>L), and right frontoparietal cortices. This model suggests an interactive network in which visual cortices and fusiform gyrus respond to the face; bodily movement is processed by the superior temporal sulcus (STS) (e.g., gaze); and both the amygdala and orbital frontal cortex modulate the ongoing processing. As an extensive discussion of the neural substrates of emotion is beyond the scope of this chapter, in addition to this brief overview, we highlight two studies that are particularly pertinent to the discussion of neural plasticity for language and emotion. The first is that of Adolphs, Damasio, Tranel, Cooper, & Damasio (2000), who investigated two aspects of emotion processing: recognition of facial emotion, and emotion labeling. Using 3D comparisons of the structural MRIs of 108 adult late-onset stroke patients, they found that those with deficits in emotion recognition were those with injury to right somatosensory cortices; and those with difficulties in labeling emotions were those whose lesions included the left operculum. They concluded that interpretation of emotional expression involves a simulation or representation of that emotion, and that emotional labels draw on left hemisphere language regions. An early set of case studies of adolescents with presumed right hemisphere damage (Weintraub & Mesulam, 1983) reported poor social skills, problems with eye contact, and flattened affect. Such findings suggest that neuroplasticity for affect may well follow a different trajectory from that of language. With these adult/adolescent profiles in mind, we now turn to the development of language and emotion expression in children with PS.

Early Language Development in Children with PS

One of the most startling early findings in the study of language development in children with PS is that, unlike adult stroke patients, in whom language is impacted far more when the stroke is in the left hemisphere, children with *either right or left* hemisphere injury were delayed in the emergence of language milestones. This delay, regardless of which hemisphere was injured, was noted early in development, in a study of infant babbling. For typically developing children, early vocalizations include cooing at about 3 months of age, and then canonical babbling (CVCV sequences) appears at about 6–8 months of age. Marchman, Miller, and Bates (1991) began following five infants with PS at 10 months of age, before they produced their first words. They report that the infants with PS were delayed in babbling compared to controls, and there was variability across both groups. However, in spite of the overall delay, the infants with PS followed a similar developmental trajectory with respect to both place and manner of articulation of consonants relative to the typically developing (TD) control group, and for both groups, consonant production was associated with word production. In the PS group, they found no differences between those with left and those with right hemisphere injury.

After the onset of canonical babbling, word comprehension is the next developmental step in language development. Early indications of word comprehension are evident in TD children about 9–10 months of age when a child turns in response to her name, or looks for the cat in response to "Where's the kitty?" First productive words then appear, on average, around 12 months of age (although there is extensive variability), with the productive lexicon increasing slowly. At about 16–18 months, a burst in vocabulary occurs as the child infers that objects have labels. It is not until 20–24 months that the first word combinations typically emerge.

Word comprehension is particularly challenging to measure in infants. Habituation/looking paradigms, which can be employed, require dozens of trials and participants; they are thus problematic for rare populations. Not surprisingly, parents offer a rich source of information regarding their toddlers' development. One successful and widely used means to chronicle early comprehension, word production, and first sentences has been the MacArthur Bates Communicative Development Inventory (MBCDI; Fenson, et al., 1993), a parental report form. In 1997, Bates and colleagues (1997) reported data from 53 children with PS (10–44 months of age) using the MBCDI. From the preschoolers, transcripts from free-play situations were also used to investigate lexical comprehension and production, as well as early word combinations. They document delay in the acquisition of each of these milestones across the group of children with PS, regardless of lesion side or site; that is, those with right or left hemisphere injury were delayed in the onset of language, word comprehension, word production, and first word combinations compared to their typically developing peers. In the context of this broad delay, they found some site-specific deficits: the infants with right posterior damage showed increased delay in comprehension, whereas those with left posterior injury were more delayed in word production. Note that this profile is unlike what might be predicted from the adult model. Results from the transcribed language samples in the toddler/preschool group (aged 20–44 months) also demonstrate an overall delay in the PS group compared to controls. In addition, they found a persistent decrement in lexical production and first word combinations as measured by MLU (mean length of utterance) in those with left posterior lesions. Again, this profile is in contrast to that of adults, where one would expect those with left frontal, not temporal, injury to have problems with word and sentence production.

A case study of a child with a large left hemisphere lesion illustrates this developmental picture. As can be seen in Figure 10.1 (A), her lesion includes frontal, temporoparietal lobes as well as subcortical structures. Note that in lexical development, her vocabulary growth reflects a similar developmental slope to that of the controls, but with a delay (Figure 10.1 B). Her use of word combinations is also significantly below that of the TD norms (Figure 10.1 C).

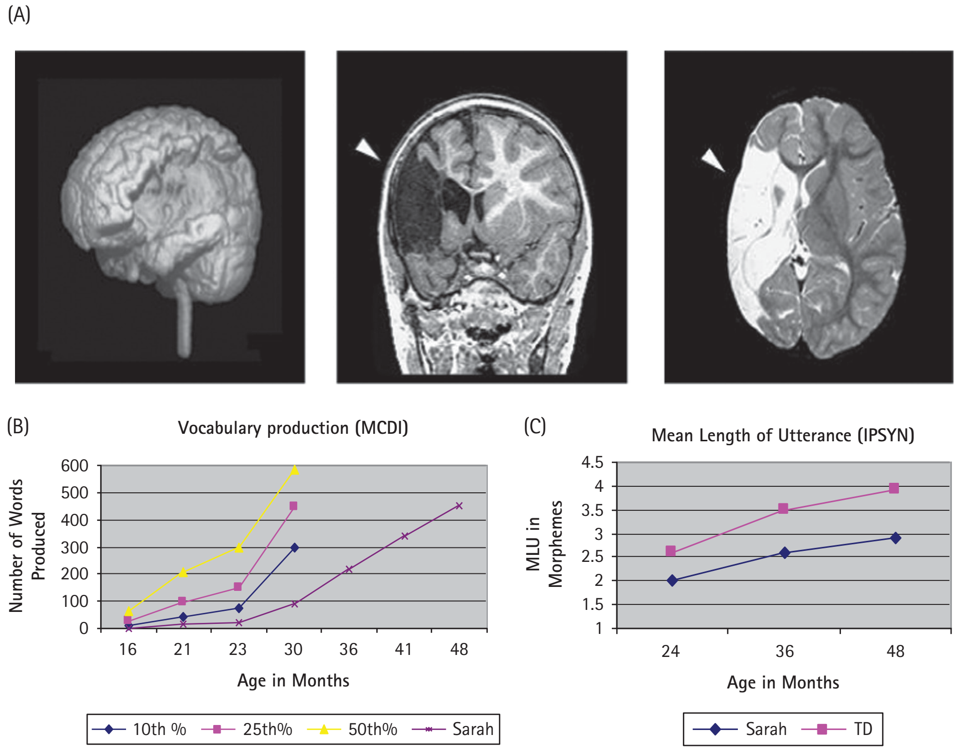

FIGURE 10.1. (A) Three views of a child's brain with a left front-temporo-parietal lesion.

Source: With permission from Moses (1999).

(B) Trajectory of this child's early lexical development as compared to a large normative sample. (C) Syntactic growth of this same child as measured by mean length of utterance. Although both lexical and syntactic development are delayed, the developmental slopes are quite similar, suggesting a late, but comparable path of acquisition.

A complementary study by Rowe, Levine, Fisher, and Goldin-Meadow (2009) also analyzed productive language from free-play sessions in a group of 27 PS and 53 TD children monthly from the age of 14 months to age 40 months. They report no differences in language performance according to laterality of lesion; however, the size and type of lesion (middle cerebral artery versus periventricular) contributed to different profiles for both vocabulary and for syntactic development. In addition to the children's language development, the authors were interested in the role of linguistic input on language acquisition. For both typically developing (TD) and PS groups, lexical growth was positively correlated with the amount of linguistic input, but for only the PS group was the use of syntax in the input associated with syntactic development. Such results have important implications for clinicians: rather than simplifying speech to make language more accessible, this study suggests that clinicians should encourage parents of children with PS to converse frequently with their child as a genuine conversational partner, and to use child-directed, yet syntactically rich sentences.

Additional studies of children with PS have confirmed the delay in the onset and acquisition of language milestones in the PS group compared to controls (Feldman 2005; Thal et al., 2004); some have additionally noted a production delay in those with left hemisphere injury (Chilosi et al., 2005; Vicari et al., 2000), while others (Rowe et al., 2009; Thal et al., 2004) have reported an overall delay and a flatter developmental slope in those with PS, without site- or side-specific profiles. Together, these results demonstrate a delay in the onset of language as well as in the acquisition of early linguistic milestones in the PS group, implying a slowed, but iterative and continued development. Importantly, unlike adults who were already proficient speakers when their strokes occurred, in the acquisition of language, the comparable delays in those with *either left or right* hemisphere injury demonstrate that children are relying on both hemispheres to acquire their native tongue.

LATER LANGUAGE IN CHILDREN WITH PS: STUDIES FOCUSED ON SPECIFIC LINGUISTIC FORMS

As children reach school age and become more compliant, targeted experimental measures and standardized tests of language are often the preferred means to assess language abilities. Standardized tests are designed to assess a child's ability to respond to specific linguistic stimuli and/or to produce targeted structures. Similar to the studies of younger children with PS, the studies using standardized tests have found no significant differences in those with left or right hemisphere injury. However, they did find that school-age children with PS as a group tend to perform behind their age-matched TD peers (Ballantyne, Spilkin, Hessleink, & Trauner, 2008; MacWhinney, Feldman, Sacco,

& Valdés-Pérez, 2000). Using a comprehensive language assessment, Ballantyne and colleagues (2007, 2008) tested children aged 5–16 years and found that while there were no differences in test performance between the children with left and right hemisphere injury, there was substantial variability in their scores, and the presence of seizures was significantly correlated with negative language outcome. MacWhinney and colleagues (2000) noted an exception to the overall poorer performance of the PS group: results from vocabulary comprehension subtests were within the normal limits. Another contrast to the low performance on standardized measures persistently reported by Ballantyne and colleagues (2007, 2008) are results from a younger group of children with PS (aged 5–6 years), which showed no difference in performance between the TD and PS groups (Demir, Levine, & Goldin-Meadow, 2010). It may well be that differences are emerging as the children acquire more complex language and are required to make increasingly subtle and complex linguistic distinctions. Alternatively, the different results may stem from the inclusion or exclusion of children with periventricular leukomalacia (PVL) in the PS group, as they tend to perform better than those with middle cerebral artery (MCA) strokes.

In addition to standardized tests, both online and offline experiments have shown the PS groups to be delayed compared to their TD peers. In English, tag questions (John likes chocolate, *doesn't he?*) are complicated syntactic structures, requiring pronoun substitution, production of the appropriate auxiliary verb, both local and long-distance verb agreement, and reversing polarity to construct the appropriate tag question. They represent a challenge for children and second-language learners as well. Weckerly, Wulfeck, and Reilly (2004) report results from a group of children with PS and their TD controls on their ability to supply the correct tag (e.g., *doesn't he?*) when given the stem (e.g., *John likes chocolate . . .*). They found no differences in performance between those with left and those with right hemisphere lesions, and they found that the PS group followed the same developmental sequence as the TD group in mastering the various aspects of tag questions: agreement, pronoun, auxiliary, and lastly, polarity. Most interesting was looking at performance across age. Whereas the PS group performed similarly to the TD controls at the younger and middle ages (4–7 and 8–11 years), in the oldest age group (12–16 years), when the TD group made substantial gains, the PS group was significantly behind their typically developing peers. These findings suggest that plasticity for later language acquisition might be limited.

Another avenue to investigate children's linguistic knowledge is to ask them to evaluate the grammaticality of a sentence. Wulfeck, Bates, Krupa-Kwiatkowski, and Saltzman (2004) performed an online grammaticality judgment task with school-age children with PS and their TD controls. For both groups of children, grammatical sensitivity increased with age, with the TD group exhibiting the adult pattern by age 11–12. With respect to reaction time, the PS group was slower than controls, and grammatical sensitivity of the PS group (while below controls) was better than adults with homologous late-onset lesions, again demonstrating the increased flexibility of the developing brain.

Standardized tests and experimental measures focusing on individual sentences or constructions evaluate a child's ability to respond to certain questions about language devoid of contextual and paralinguistic cues. However, they do not tell us how well a child uses language in his or her everyday life. In fact, in typically developing children aged 7–14 years, we found little correlation between a child's performance on standardized measures and his or her performance in natural language situations (Reilly & Polse, 2016). For a broader perspective on language development, we next review studies that focus on language production in more naturalistic discourse situations.

Later Language Development in Children with PS: Discourse

By age 5, typically developing children are proficient language users and have access to a repertoire of grammatical structures, although language development continues well into adolescence (Berman & Verhoeven, 2002; Nippold, 1998; Reilly, Zamora, & McGivern, 2005). Later language development involves not only an increasingly wide vocabulary and access to more complex structures, but also a growing ability to flexibly recruit and employ such structures for various discourse purposes. As they enter primary school, children can participate in a conversation, describe pictures and events, and are beginning to tell coherent stories. To better understand later language development in children with PS and its resilience as discourse requirements become more challenging, in this section we review a series of discourse studies that reflect increasing cognitive demands: dyadic conversation, telling a story from a picture book, and personal narrative.

A dyadic conversation represents the earliest discursive genre for children; in fact, dyadic interactions begin early in the first year, well before first words are produced, with children showing conversation-like turn-taking in their early vocalizations, gestures, and behaviors (e.g., playing peek-a-boo) (Bruner, 1975; Stern, 2009). Rather than reflecting a broad structure, in a conversation, interlocutors respond to the preceding utterance or turn, and the partner reciprocates. As such, conversations are locally organized by turns. In 2001, Bates and colleagues (2001) used a semi-structured interview to compare the conversational discourse of 38 children with PS (aged 5–8 years) and their TD controls to 21 adults with homologous late-onset unilateral strokes and their neurotypical adult peers. The adult stroke patients broadly followed the classical profile: those with left hemisphere injury who were severely aphasic produced fewer utterances, had lower syntactic diversity, and made more morphological errors and omissions than their controls; those with Wernicke's aphasia were characterized by neologisms and lexical substitutions. As expected, those with right hemisphere injury made few linguistic errors. However, they produced twice as many propositions as controls, and their speech tended to be disinhibited and lacking in content. The children with PS presented a distinctively different profile. Unlike the adult stroke patients, the children with PS performed comparably to their TD peers on all linguistic measures. There were no differences between those with left or right hemisphere injury and, importantly, the language of the PS group was similar to that of the TD group with respect to vocabulary, morphological proficiency, and in recruiting complex syntax. Figure 10.2 compares (A) morphological errors and (B) the frequency of recruiting complex sentences across the groups. In form, these interviews represent a quasi-naturalistic context for the evaluation of spontaneous conversational language; as such, they are the age-appropriate equivalent to the "free-play" sessions used with younger children described in the research presented earlier. Performance in these interviews is evidence that the earlier noted deficits in the PS group have resolved and that by early school age, the children with PS appear to have "caught up" to their peers in productive conversational language.

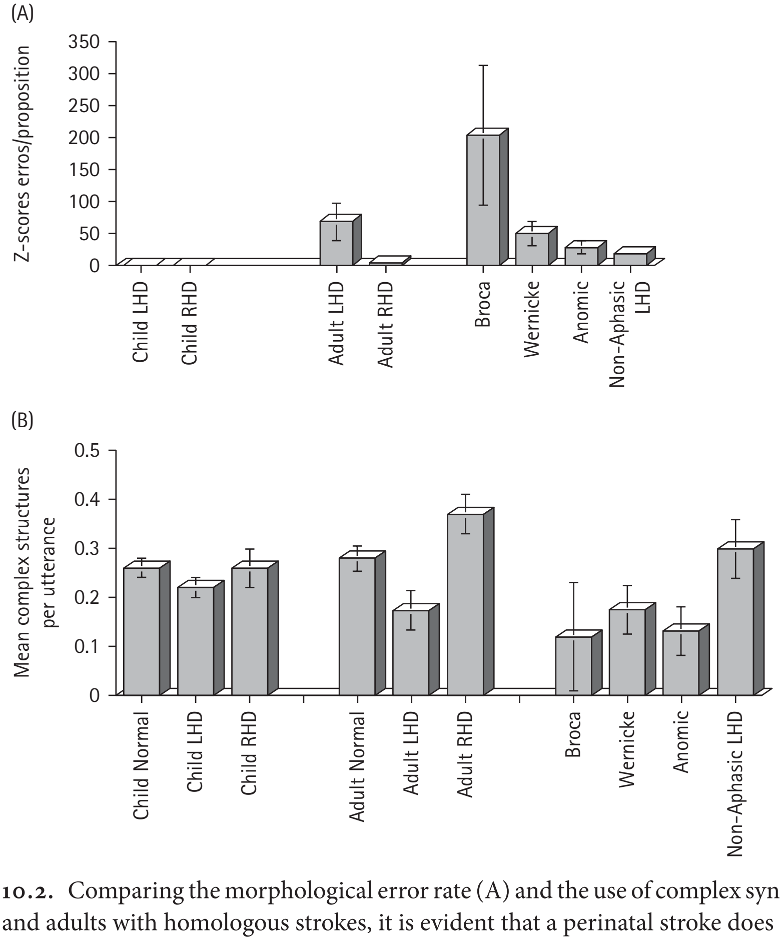

FIGURE 10.2. Comparing the morphological error rate (A) and the use of complex syntax (B) in children and adults with homologous strokes, it is evident that a perinatal stroke does not exact the same devastating effect as a late onset stroke.

Source: Reprinted with permission from Bates et al. (2001).

To extend our understanding of discourse, we asked some of these same children (and some older and younger) to tell a story from a picture book, *Frog, Where Are You?* (Mayer, 1969; see Berman & Slobin, 1994, for a review of typical narrative development). Unlike conversations, stories have a canonical structure: good stories have a setting, a problem, an attempt at resolving this problem, and a conclusion or resolution. As such, they represent a cognitively more challenging task than a conversation, as the child must plan, as well as integrate the local events of the story with the overall theme. The story, *Frog, Where Are You?* is a traditional "quest story": a boy has captured a frog who then escapes. The hunt for the missing frog includes encounters with other animals until the frog (and its mate and babies) are discovered by the boy (and his dog). In narrative development, typically developing children have some idea of "story" by their third year (Appleby, 1978); by age 5, children tend to produce horizontally linked narratives using "and" and "and then" to sequentially relate events. It is not until about 8 years of age that children are able to integrate the horizontal (local) episodes with the overarching theme (e.g., searching for the frog).

The Frog Story studies of children with PS (Reilly, Bates & Marchman, 1998; Reilly et al., 2004) included 52 children with PS and age- and gender-matched controls from 3;11–12;3 years of age. The children's stories were evaluated for both linguistic measures, for example, morphosyntactic errors, use and diversity of complex syntax; as well as discourse features, for example, whether the search theme was articulated, and whether the child included all the story components. Consistent with earlier studies, the first finding was no difference between those with right and those with left hemisphere injury on any linguistic or discourse measure after age 5.[1] Looking at their performance as a group, the stories from the children with PS were shorter than those of the TD group. The children in the younger and middle PS groups (aged 3; 11–6; and 7–9) made more morphosyntactic errors and used less complex syntax, as well as fewer syntactic types than their TD peers, but both groups made fewer errors and produced more complex sentences as they got older. To give a flavor of the children's language, Box 10.1 presents an excerpt from a Frog Story from Sarah (from Figure 10.1) at ages 4;11 and 8;2.

It is important to note that the morphosyntactic errors of the PS children are the same types of errors seen in the speech of younger TD children, suggesting that children with PS are following a similar path in acquiring English to their TD peers, but at a slower pace. For these linguistic measures in the narratives, it was not until age 10 that the performance of the PS group matched that of their TD peers. It appears that a story from the picture book challenges the language capacities of the PS group (as measured by grammatical proficiency) more than those of the TD children. However, in this discourse context, children with PS seem to have "caught up" to their TD peers by 10 years of age, a few years later than was observed in a less challenging, dyadic conversational context.

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[1] (The four children under age 5 years whose lesion affected the left temporal lobe had made more morphological errors than their age mates, but this difference was no longer present after age 5.)

Box 10.1. Excerpts from the "Frog Story" from a child with LPS.

Narrative excerpts from a child with Left Perinatal Stroke (LPS) telling, *Frog, Where Are You?* (at ages 4;11 and 8;2).

4;11:

'The boy's looking at fwog. Then the dog... began to bark. Then the fwog...he comed out. Then the dog and the boy couldn't see the fwog! He woked up. He looked outside. Then the dog fell down. Then the, then the boy got pushed. Um . . . he screamed."

8;2:

"The boy and the dog are looking at the frog. The boy is sleeping on his bed and the frog got out. And when the boy woke up, the frog was gone. He was peeking in his vest, and he was calling the frog. And then the dog fell out, fell through the window. He was mad. He was yelling really really really loud."

With respect to the more global discourse measures of narrative, although they include more story components with age, the stories from both older and younger children in the PS group included fewer episodes than those of the TD group, even though they were all telling the same story with the picture book in front of them. Children in both TD and PS groups were likely to remark that the frog had initially disappeared; however, the children with PS were less likely to mention that the boy's activities (e.g., looking in the tree) were motivated by his search for the frog; that is, the PS group was less likely to present a goal or theme of the story to render the story cohesive. In a qualitative analysis of the texts from all the 7- to 8-year-olds (both TD and PS), the stories were classified into three groups (High [best stories], Middle, and Low) based on such elements as plot, elaboration, reference, and "storiness," which was defined as "use of linguistic connectors to integrate events." The stories in the Low group were all from the PS children (with one exception), whereas all the highest scoring stories (High group) were from the control group, except for one. In sum, although stories from both groups were more complete and complex in the older groups of children, the stories from children with PS were less cohesive and more impoverished than those of controls overall.

In the dyadic conversation data presented above, the language of the PS group was comparable to that of their TD peers at age 5; in the picture book narrative, it was not until age 10 that their morphological proficiency and use of syntax was similar to the TD group. The differences in their performance on the picture story narratives compared to that of the interviews suggests that language is more fragile for the children with PS than for the TD children, and that discourse context and cognitive complexity are influential factors in the quality of their language performance.

It is clear from these studies that children with either right or left hemisphere lesions are affected in language development and that language in the children with PS is delayed. However, it is also evident that their language continues to develop and appears to be following a similar behavioral path to that of typically developing children, but on a somewhat different time schedule. Discourse context and cognitive demands also appear to have a greater impact on language performance in children with PS than in typically developing children. Together, these findings raise questions regarding the nature of later language development in the PS group. Will they continue to make progress and finally "catch up" to their age mates in all linguistic contexts? To address these questions, we now turn to an even more challenging discourse context—personal narratives—as we follow language development into adolescence. In contrast to the picture book, where the story is provided, in the case of a personal narrative, it is the child's responsibility to recall, organize, and recount events from his or her life into a narrative. Although a common occurrence in quotidian life, recounting a personal narrative draws on a range of social, linguistic, memorial, and organizational skills.

Children and adolescents were asked to "[t]ell about a time when someone made you sad or angry; what happened, how it began and how it ended" (Reilly, Wasserman, & Appelbaum, 2013). Ninety-five children participated (20 LPS, 15 Right Perinatal Stroke (RPS), and 60 TD). Children were divided into a younger (7–11 years) and an older (12–16 years) group, and similar to the picture stories, the children's transcribed texts were assessed for both linguistic and narrative measures. Linguistic measures included Productivity, Morphological Errors, and Complex Syntax; narrative measures included Setting (Time, Situation, Characters, and Location), and story components (Setting, Problem, Attempt at Resolution, Resolution). On the language measures, the PS group as a whole performed more poorly than their age-matched TD peers, and those with left hemisphere lesions fared the worst. The children with left hemisphere injury made more morphological errors and used fewer complex sentences and sentence types than the controls. Those with right hemisphere lesions did not differ significantly from controls on these measures, but their average morphological error rate and frequency of complex syntax fell between those with LPS and the TD group. With respect to the narrative components, all the children produced stories with the requisite components. However, those with LPS produced more impoverished settings than controls, whereas those from the RPS group did not differ from the TD group. Including a Setting to introduce one's story is a developmentally later acquisition; socially, it orients the listener and establishes the world in which the story will unfold. As such, for these older children the quality of the setting has proven to be a sensitive measure of later language development (Tolchinsky, Johansson, & Zamora, 2002). The children in this study ranged from 7 to 16 years of age, and we found that children in the older TD group made significantly fewer errors and produced richer story settings than the younger TD group. Surprisingly, however, there were no comparably significant developmental differences in the younger and older LPS and RPS children. One reason for this lack of apparent change with age in the PS group may well be the elevated level of variability in their data. To illustrate this variability, Figure 10.3 represents the morphological error data from the older and younger TD, LPS, and RPS groups.

Variability characterizes the early stages of language acquisition in typical development. For example, assessing morphological proficiency in spontaneous speech, children aged 3 and 4 years show high variability: some make numerous errors (e.g., more than one error per clause), whereas other preschool-age children are making few errors

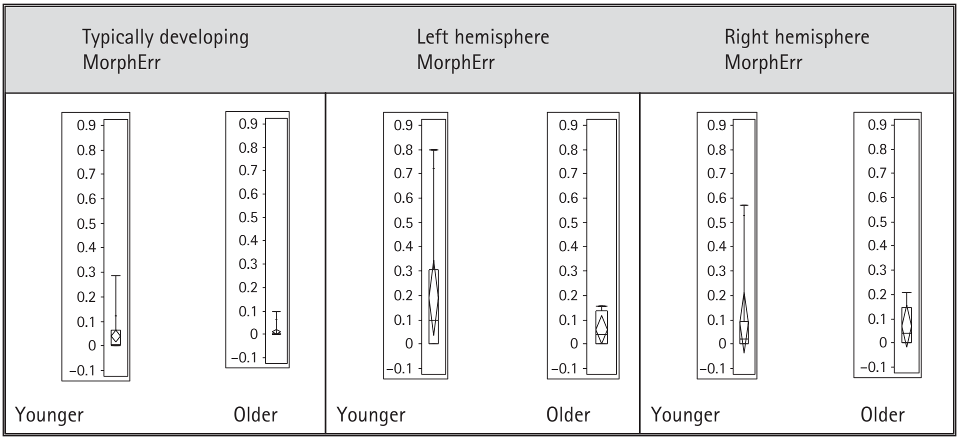

FIGURE 10.3. Variability in morphosyntactic errors. The older groups in all three populations make fewer errors than their younger counterparts, but the variability of the children with brain injury, both those with LPS and RPS, far outstrips that of the TD group.

Source: Reprinted with permission from Reilly, Wasserman, & Appelbaum (2013).

(e.g., one error per every 10 clauses). However, by about age 5, typically developing children make few errors, averaging one error every 10 clauses in spontaneous speech; and by age 10, TD children are making about one error per 20 clauses in spontaneous speech (Reilly et al., 2004). As such, the early pattern of variability becomes increasingly homogenous as children master the morphology. Consequently, if an 8-year-old were making significantly more errors than his or her peers, he or she would be a candidate for clinical evaluation. In contrast to school-age typically developing children, the extensive variability in language performance in the PS group has been noted across studies and research groups (e.g., Feldman, 1994; Marchman et al., 1991; Reilly et al., 2012, Rowe et al., 2009; Thal et al., 2004), and makes it difficult to determine linguistic norms for this group. What might underlie this broad variability? We address this question later in the discussion.

Personal narratives from children with PS provide an additional perspective on later aspects of language development: those with RPS performed somewhat lower, but did not differ significantly from controls on either linguistic or discourse measures; however, those with LPS performed worse than controls in all areas. In this more challenging discourse genre, it appears that the language of the PS group (and especially of those with left hemisphere lesions) is more vulnerable than that of the TD group. Moreover, the results bring into relief the increased fragility of productive language for those with left hemisphere lesions, whose performance subtly mirrors adults with homologous late-onset stroke.

To briefly summarize language acquisition in children with PS, language onset is delayed, as is each of the early developmental milestones: babbling, word comprehension, word production, first word combinations, and the acquisition of morphology. Within this broad landscape of delay, studies have found some site-specific characteristics: early on (ages 10–17 months), those with right posterior injury showed greater comprehension deficits than others in the PS group, and those with left hemisphere injury reflected greater delays in word and early sentence production. However, these side-specific profiles appear to resolve by about 5 years of age. Whereas the language of the PS group was initially characterized by delay and development, by early school age (5–8), the PS group performs comparably to their age-matched controls with respect to lexical diversity, morphological proficiency, and in employing complex syntax in conversation. At this age, TD children are considered to have "acquired" the basic structures of their language (Slobin, 1985, 1992, 1997), and from the acquisition literature on TD children, we would predict relative stability across naturalistic contexts. As we saw from the two narrative studies presented earlier, this is not the case for the children with PS. In contrast to the biographical interview, in the Frog Story, it is not until age 10–12 that the PS group performs comparably to controls on morphological and syntactic measures. Such findings suggest that the added cognitive task of inferring a story from pictures challenges their language abilities, and that their language is more fragile than that of the TD group. In reviewing data from the more demanding personal narrative, not only are the PS stories more impoverished and more errorful than those of their TD peers, but it is the children and adolescents with left hemisphere injury who fare the worst. These findings may constitute evidence of limits on neuroplasticity for spontaneous language; moreover, they suggest that the left hemisphere may indeed be privileged for language.

PROFILES OF AFFECTIVE EXPRESSION IN CHILDREN WITH PS

As noted earlier, by their first birthday, when first words emerge, TD infants are already good affective communicators. They use facial expression, gesture, and affective vocalizations to convey their desires and to interpret the behavior of others. Moreover, they can initiate and participate in, first, dyadic and then triadic interactions using these nonlinguistic tools. The early developmental appearance of this communicative system affords another perspective on development and neuroplasticity.

In our first study of emotional expression in infants with PS (Reilly, Stiles, Larsen, & Trauner, 1995), we asked mothers to play with their pre-linguistic infants (6–22 months of age) as they did at home. Mother-infant dyads were video- and audio-taped with multiple cameras to capture the faces, language/vocalizations, and behaviors of both participants. The results were surprising. As can be seen from Figure 10.4, the typically developing infants demonstrated a range of positive responses to their mothers' bids for attention: some infants were very smiley and others more serious, but overall they smiled easily. Those infants with posterior left hemisphere lesions clustered tightly in the mid-range of "smiliness" compared to the typical group, whereas those with posterior

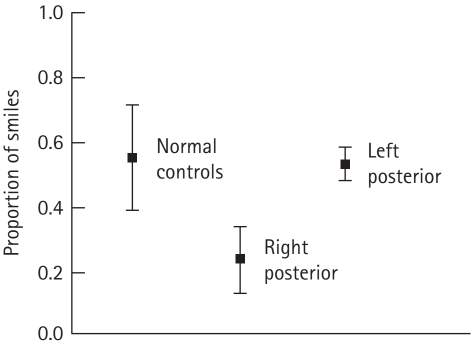

FIGURE 10.4. Infant smiles in response to maternal bids for conversation. Whereas TD infants show a range of "smiliness," those with LPS cluster tightly in the mid-range of the TD group; in contrast, those with RPS fall below those with TD and LPS in their frequency of smiles.

Source: Reprinted with permission from Reilly, Stiles, Larsen, & Trauner (1995).

right hemisphere lesions smiled significantly less frequently than either the TD or LPS groups (see Figure 10.4).

Moreover, the RPS group also produced more negative vocalizations than either the controls or those with LPS. In sum, whereas those infants with left hemisphere lesions cluster with controls for both affective facial and vocal expression, the infants with RPS smile significantly less frequently and produce more negative vocalizations than their LPS and TD peers. A complementary parental report study on young children with PS (Nass & Koch, 1987) that used a temperament questionnaire reported similar results: those toddlers with RPS displayed more negative expressive behaviors than those with LPS or the TD group, and this profile continued into preschool. Such findings are consistent with affective expression in adults with late-onset right hemisphere stroke. Blonder and colleagues have reported a series of studies depicting the spontaneous use of facial expression and prosody in adults with stroke in conversation (Blonder et al., 1993; Blonder et al., 2005). They found a decrement in affective expression overall, as well as increased negativity and a decreased expression of positive emotion in adults with right hemisphere damage (RHD)compared to neurotypical adults and those with left hemisphere damage (LHD). As such, unlike the emergence of language where the developmental profile contrasts with that of adults, that is, children with *both* right and left hemisphere lesions show considerable delay, the profile for affective expression (both facial and vocal) in the PS group mirrors that of adults. Such findings suggest that the neural underpinnings for affective expression are established very early, sometime in the first year of life. The question that arises concerns plasticity and development: what is the nature of the affective profile of the children with RPS as they develop and as they acquire language?

To address this question, we returned to the biographical interview data of 20 children with PS aged 5–6 years (10 RPS, 10 LPS, and 20 TD) (Lai & Reilly, 2015). This context is most similar to free play with infants and the conversational context in the Blonder studies, thus affording an appropriate comparison. The videotapes were analyzed for facial expression production and the transcribed texts for the content and affective valence of the children's utterances. Similar to their infant and adult counterparts, the children with right perinatal stroke used less facial expression overall during the interview than either those with left hemisphere lesions or controls; moreover, they also used less affective language than with those with LPS or the TD group. In assessing the valence of their speech, whereas both the TD and LPS groups relate mostly positive experiences in the interviews, those with RPS recount slightly more negative than positive experiences. It must be noted here that the children with RPS can tell stories about emotional events and did so reasonably successfully in their personal narratives discussed earlier. It is rather that spontaneously they do not express emotion with the same frequency or the same valence as their LPS or TD peers.

To summarize our findings on spontaneous production of emotional expression in children with early stroke, we found that from early in infancy, those with LPS cluster with their typically developing peers, while those with RPS express less positive affect overall, as well as more negative affect than either those with LPS or their TD peers. This profile mirrors that of adults with late-onset homologous lesions. As these children develop and acquire language, we continue to see an analogous profile in which those with right hemisphere lesions persistently express less emotion overall, with a tendency toward negative affect. Interestingly, this profile extends to facial expression and vocalizations, as well as to the content of spontaneous language. The most striking aspect of the school-age profile for emotional expression in the PS group is the apparent lack of development or change up through age six years. Similar to their infant patterns, the school-age children continue to mirror the adult profile in their spontaneous use of affective expression; that is, unlike the slower, but steady development of language in children with PS, their affective profile remains relatively stable, with those children with RPS demonstrating a persistent decrement in emotional expression, especially positive expression. What might explain these contrastive developmental profiles? Considering the development of the neural substrates of these two communicative systems (language and affect) in typically developing children may provide clues to this question. The following sections are thus devoted to what we currently know about the development of the neural bases of language and emotion in infants and children.

Neural Organization for Language in Childhood

Neuroimaging evidence suggests that early in development, at 3 months of age (following approximately 4 months of language exposure in utero), infants show some left-lateralization for language in response to forward versus backward speech (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). By 12–18 months, they are recruiting left frontotemporal networks in the left hemisphere (similar to adults) in response to a single word matched with a picture (Travis et al., 2011). When considered in light of these neuroimaging results, it is not surprising that children with left hemisphere perinatal stroke, who lack the neural tissue to support this same early lateralization pattern, are delayed in early language milestones relative to typically developing children and children with right hemisphere lesions. It *is* somewhat surprising, however, that children with right hemisphere injury also show delays in initial language milestones such as babbling and producing their first words (e.g., Bates et al., 1997; Marchman et al., 1991); that is, if word recognition in the first year and a half recruits primarily left hemisphere anterior areas, why do we see a delay in this skill particularly in children with right posterior injury? Pediatric neuroimaging research that takes into account both language proficiency and development sheds some light on this apparent enigma.

Using event-related potentials (ERPs; see Leckey & Federmeier, Chapter 3 in this volume), Mills, Coffey-Corina, and Neville (1997) reported that in typically developing infants 13–20 months of age, known words elicited larger amplitude ERPs at 200–400 milliseconds following word onset relative to nonwords. In the younger half of the sample (13–17 months), this amplitude difference was observed bilaterally over frontal, temporal, parietal, and occipital electrodes. By 20 months, however, the difference occurred mostly over left hemisphere temporal and parietal sites. Importantly, the older infants in the sample (20 months) who knew more than 150 words elicited more focal ERPs over left hemisphere electrodes, whereas the 20-month-olds who understood fewer than 50 words elicited more distributed ERPs over bilateral electrodes. This research suggests that initially, word processing is more distributed and is processed bilaterally; it is only with age *and* increasing vocabularies that word comprehension becomes more focally organized in left hemisphere perisylvian regions. Together these neuroimaging results provide a context for understanding early language development in children with PS, and demonstrate that lateralization for language is a dynamic developmental process, one highly dependent on language acquisition itself. Such results are consistent with the finding that children typically recruit both hemispheres in the initial stages of word acquisition and thus, both children with left hemisphere lesions and children with right hemisphere lesions show an initial language delay.

As children grow older, language quickly becomes more than the production and comprehension of single words. Their vocabularies expand, and they begin to string words together, first into simple and then into syntactically complex sentences. These more complex linguistic processes require broader cognitive faculties that recruit bilateral neural networks. There is now ample evidence that as children develop through the elementary school years and into adolescence, these bilaterally distributed neural networks for language become more localized to left hemisphere perisylvian regions (e.g., Booth et al., 2003; Brown et al., 2005; Holland et al., 2001; Schlaggar, Brown, Lugar, Visscher, & Miezin, 2002; Schmithorst, Holland, & Plante, 2007; Szaflarski, Holland, Schmithorst, & Byars, 2006). Importantly, this shift is not dependent on age alone, but also depends on the task (i.e., what aspect of language is probed), the child's proficiency with that linguistic element, and the area of the brain recruited for a particular linguistic task.

In a covert semantic fluency task with adults and children, Gaillard and colleagues (2003) found left lateralization for a lexical task by age 7, with no differences between child and adult lateralization activation. However, another functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume) investigation by Holland and colleagues (2009) of children aged 5–18, which probed multiple aspects of language processing (lexico-semantic, syntactic, prosodic), found that it was the later acquired (more complex) aspects of language (i.e., syntactic tasks without semantic content) that had more bilateral representation in the developing brain. Earlier acquired (simpler) language functions, such as lexico-semantic tasks (measured by a word-picture matching), on the other hand, showed stronger left hemisphere lateralization, which was significant in both anterior and posterior areas. An additional fMRI investigation using spoken, rather than covert, responses in a verb-generation task provides further evidence that the lateralization process is progressive; it is not only dependent on task, age, and brain areas recruited, but also on the level of proficiency with the language structure assessed (Brown et al., 2005). Brown and his colleagues also noted that during this developmental process of lateralization for language, activation in areas associated with earlier processing "lower-level" mechanisms (e.g., bilateral occipital and temporal cortex) decreased in the older children, concomittant with increases in activation in left frontal and parietal cortex (regions associated with "higher-level" top-down control).

It is clear that the language system, unlike other communicative systems such as affect, has a remarkable capacity to exploit neural plasticity, and the preceding discussion provides a possible explanation for the remarkable language development in children with PS. However, it is not clear *how* the brain responds to an early insult; that is, what neural tissue are these children recruiting for language use? Some studies suggest that for those with left hemisphere injury, the remaining healthy neural tissue in the left hemisphere takes on language functions (Liegeois et al., 2004; Saccumen et al., 2006). Additional research indicates that homologous right hemisphere regions more often support language processing (Holland et al., 2009; Jacola et al., 2006; Staudt et al., 2002; Szaflarski et al., 2014; Tillema et al., 2008). Additional investigations have found evidence for both: In one of the few imaging studies with children with PS, Raja Beharelle et al. (2010) found that language performance was positively correlated with left lateralization in the inferior frontal gyrus and bilateral activation in the superior temporal regions. These apparently contradictory results between investigations may reflect the variability in language function, as well as the variability in neural organization that is characteristic of this population. An imaging study by Fair and colleagues (2009) confirms that each child with a left perinatal stroke recruits a unique and individual right hemisphere network in response to lexical stimuli. In sum, it is likely that the distributed, bilateral language network in typical childhood provides these children the opportunity to exploit ipsilateral neural substrates surrounding the lesion, as well as contralateral homologous tissue (which are typically involved in language processing in childhood) to support language. This period of bilaterality for language may well contribute to the high degree of neural plasticity and development observed in language in this population, which contrasts with the development of communicative affect.

Neural development is a dynamic process, with each step laying the foundation for the emergence of new neural structures and systems (Stiles, 2008; Stiles, Brown, Haist & Jernigan, 2013). Thus, it is the iterative nature of development itself that dictates the functional and structural organization of a child's brain. For the children with PS, therefore, it is not only the event of a cerebral injury, but the way in which this event impacts successive brain development that determines the neuroanatomy for and proficiency of language. We next consider the neural underpinnings and development of affect and emotion.

Neural Organization for Processing Emotional Facial Expression in Infancy and Childhood

In contrast to the burgeoning pediatric neuroimaging literature for language, the parallel literature on emotion is more limited, with the majority of investigations focusing on face processing. As processing faces is imperative to understanding emotional facial expression, this literature will be briefly discussed.

From behavioral studies (see Herba & Phillips, 2004, for a review of emotion development and Pascalis et al., 2011, for a review of face processing) we know that processing faces and emotional facial expression, as well as the neural underpinnings involved in face and emotional face processing (Batty & Taylor, 2006; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Gee et al., 2013), continue to develop well into adolescence and young adulthood. However, it appears that very early in development, the infant brain is already attuned to faces and to the information they provide (Grossman & Johnson, 2007). Newborn infants attend to face-like patterns, and such behavior is supported by a subcortical neural network (Johnson, 2005). Evidence for the prenatal development of such subcortical connections, and their role in affective development, stems from studies of nonhuman primates. After lesioning the amygdala in rhesus monkeys during the neonatal period, as adults, these monkeys showed significantly blunted affect, with decreased responses to both positive and negative stimuli (Bliss-Moreau, Bauman, & Amaral, 2011).

With respect to face processing, ERP studies in human infants, aged 3–12 months, show activation of left and right lateral occipital areas, the right fusiform face area (FFA), and the right superior temporal sulcus (STS) in discriminating upright and inverted faces (Johnson et al., 2005). In addition, in a rare imaging study of a small group of 2-month-old infants, Tzourio-Mazoyer and colleagues (2002) found that in response to faces (versus colored lights) a network comparable to the core adult system for face processing was activated in the infants' brain, including the right inferior temporal gyrus (the infant homologue of the adult fusiform gyrus), bilateral occipital, and right inferior parietal cortices. They also found activation of left superior temporal and inferior frontal gyri, areas typically associated with language processing in adults. Together these studies suggest that a face-sensitive neural network is functioning in the first months of life, and although broader than that of adults, many of the specified areas are also implicated in the adult face-processing network (Haxby, Hoffman, & Gobbini, 2000).

Studies investigating infants' responses to emotional facial expressions show that by 7 months of age, infants respond differentially to fear and happy/neutral faces, (Nelson & de Haan, 1996; Leppänen & Nelson, 2008). However, responses did not distinguish between angry and fearful faces (Nelson & de Haan, 1996), suggesting that emergent emotional categories are broad and reflect simple positive/negative parameters. Batty and Taylor (2006) report a developmental ERP study on the neural bases of emotion processing in children and adolescents (ages 4–15). Their study follows changes of P1 and N170, components associated with face and emotional processing in adults. In the children, the P1 was sensitive to faces across childhood, and by age 4, the N170 was also face sensitive. They found decreases with age in both the amplitude and latency of the P1, suggesting increased automated visual processing for faces. The P1 latency showed an effect for emotion even in the youngest children; in contrast, the N170 was only sensitive to emotion type in the oldest group (14–15 years). These results indicate that even though infants and young children use emotional facial expression fluently and frequently, their neural bases reflect a protracted developmental course well into adolescence.

Using fMRI to look at emotion responsivity, an early pediatric imaging study investigated amygdala response to fearful faces in children (average age: 11 years) and adults (Thomas et al., 2001). They found differential response patterns: Whereas adults demonstrated increased left amygdala activation to fearful over neutral faces, the children showed greater amygdala response to neutral than fearful faces. A complementary study by Todd, Evans, Morris, Lewis, and Taylor (2010) with children 3;6–8;6 showed that unlike adults, the children showed increased amygdala response to happy over angry faces, but that amygdala activation to angry faces increased with age. Recently, several pediatric neuroimaging studies of emotion processing have focused on amygdala-prefrontal connectivity. The results from Gee et al., (2013) and Swartz et al. (2014) suggest that with development, increased structural connectivity is related to decreased amygdala activation in response to sad and happy faces, and that such increased connectivity affects the development of emotion regulation. Together these studies attest to the extended development of the neural bases for emotion and its regulation, indicating refinements in function and connectivity that continue to develop beyond childhood.

Despite this protracted development, a nascent neural network for face and emotion processing is present early in the first months of life, perhaps at birth, and this network recruits both cortical and subcortical structures that are implicated in the mature adult network. As such, a pre- or perinatal stroke involving the posterior regions of the right hemisphere may well have long-term consequences for their development.

Conclusions

An accruing literature has noted that language function is especially resistant to neural injury early in life, and has concluded that language enjoys a particularly high degree of neural plasticity in childhood. The data on affect extend and refine our understanding of neuroplasticity for communicative systems more broadly. The remarkable development of language in these children with either right or left hemisphere injury as compared to the specific deficits in affective expression that are associated with lesion site bear witness to the range and limits of neuroplasticity of the developing brain. Possible explanations for these gradients of plasticity may stem from the intersection of phylogeny and ontogeny.

Relative to language, the affective system is evolutionarily old. Even in lower animals, we see evidence of affect: an angry tortoise will bob his head repeatedly on sighting another tortoise whom he perceives as a threat; prairie voles show affiliative behaviors toward their lifelong mates. As such, evolutionarily "older" brain structures, such as the visual cortices and limbic system, support affect, while language processing recruits relatively newly evolved cortical structures, such as regions in the frontal and prefrontal cortex. It is likely that these early affective brain structures are less flexible and more constrained than later evolving cortical regions. As such they may well be less capable of co-opting alternate neural tissue to adapt and reorganize following injury. In addition to being a more evolutionarily primitive system relative to language, communicative affect also emerges earlier in development than either expressive or receptive language.

With respect to ontogeny, it is not until later in the first year of life that infants show some understanding of language, suggesting that the neural circuitry involved in language processing for communicative purposes is just beginning to function. As we have noted, the neural substrates recruited for language in childhood are broadly distributed across both hemispheres in typical development. This distributed state provides a natural opportunity for children with PS to strengthen and refine supplementary pathways in ipsilateral surrounding and contralateral homologous brain regions to support language. By late adolescence, when typically developing language has become more focally organized in the left hemisphere (Szflarski et al., 2006), children with PS have co-opted these early additional neural pathways, and have established them for language. For adults with late-occurring stroke, language has already lateralized to the left perisylvian regions. As such, they have missed this natural developmental period of bilaterality for language, and thus do not have the same opportunity to capitalize on naturally existing alternate cortical circuitry.

In contrast to language, the onset of emotion and affective communication emerges just after birth, with infants producing facial configurations respecting canonical emotional expressions when they are only a few days old (Oster, 1978). Critical to emotion and face processing are subcortical networks including the amygdala (Adolphs 2003; Johnson, 2005). Johnson has proposed that the subcortical neural substrates involved in early emotional processing may be established prenatally, and support for this hypothesis comes from research from nonhuman primates. Thus, like the adults with late-occurring stroke who have missed the opportunity to utilize naturally existing distributed networks for language, the opportunity to develop and strengthen more distributed neural substrates for face and emotion processing may be significantly decreased because critical aspects of the neural tissues that support such processing are already active at birth. This early neural specification for emotion processing may explain the similarity of the affective profiles between children with PS and adults with late-occurring stroke.

The preceding discussion sheds some light on the gradients of neuroplasticity in different communicative systems, and suggests that the interaction between ontogeny and phylogeny plays a critical role. For language, it is clear that early-occurring perinatal strokes do not produce the same irreparable damage that we witness in adults with homologous late-onset strokes. Furthermore, for the children, the side of the lesion has relatively little impact on their behavioral linguistic profile, whereas in adults, the side and site of the lesion are good predictors of language function following stroke. If we look uniquely at language and its acquisition, it appears that plasticity of the young, developing brain reflects the possibility for extensive (re)organization following a neural insult. However, our findings on affect, a complementary communicative system, indicate that children with early injury show similar, albeit more subtle, effects from their early stroke to those of their adult counterparts. These distinctive profiles and developmental trajectories for language and affect demonstrate that the processes underlying neural organization (i.e., plasticity) do not operate indiscriminately; these processes are inherently tied both to functional neuroanatomy and development itself.

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CHAPTER 11

THE NEUROLINGUISTICS OF BILINGUALISM

Plasticity and Control

DAVID W. GREEN AND JUDITH F. KROLL

INTRODUCTION

LANGUAGE use is a form of communicative action, and the languages we use complement and extend our ability to act jointly with others. To achieve our communicative goals, we recruit diverse representations and skills. In a conversation, for example, we recruit skills in reading mental states, drawing inferences, and mapping experiential states into spoken words. For many of us, achieving our communicative goals involves using more than one language over the course of the day. Our contention is that the nature of such usage exerts profound effects on the brain.

Strikingly, bilingualism appears protective of cognitive decline in the elderly (Bak, Nissan, Allerhand, & Deary, 2014; see also Kavé, Eyal, Shorek, & Cohen-Mansfield, 2008, and Perquin et al., 2013, for data on multilingual speakers) and delays the onset of dementia relative to monolingual samples by an average of 4–5 years independent of socioeconomic status, immigration status, or language type (Alladi et al., 2013; Bialystok, Craik, & Freedman, 2007; Woumans et al., 2015; see Bak, 2016, for a discussion of possible counter-evidence and an appraisal of potential confounds). It also appears predictive of cognitive function post-stroke (Alladi et al., 2016). Such neuroprotective effects plausibly derive from the adaptive changes required to represent and use two languages. Why should there be adaptive changes?

We have no theory yet of how the use of more than one language changes the brain and on how such changes may affect even nonlinguistic performance. Instead, we start from a single premise and explore the questions that arise from it and the neural data that bear on them. Our premise is that the use of more than one language imposes additional demand relative to the use of a single language. It is this increased demand, and how it is met, that drives plastic change. Our premise gives rise to two immediate questions: What kinds of demand are there? How might the brain respond to increased demands? We consider these questions in the next two sections.

Two Types of Demand

We can think about the nature of the demand by distinguishing between the language network that captures a person's knowledge of each language (e.g., its syntactic patterns and vocabulary) and how it is used (the network or circuits involved in language control). By "control processes" we refer broadly to processes that allow individuals to perform a range of language tasks (e.g., naming a picture rather than describing it), making a request or issuing a command, and speaking one language rather than another.

Neuropsychological data not only support the face validity of the distinction between the language network and its control, but also indicate that control processes are essential to normal language use. In bilingual speakers, stroke damage can impair some aspects of language control while sufficiently sparing the language network (Green, 1986). For example, Fabbro, Skrap, and Aglioti (2000) reported the case of an Italian-Friulian speaker (S. J.) whose lesion included the left prefrontal cortex, part of the anterior cingulate, and the left striatum. Clausal processing for speech comprehension and production was intact for both languages, but S. J. was unable to avoid switching into Friulian (his L1) even when addressing an Italian speaker who spoke no Friulian. Likewise, when required to speak Friulian only, S. J. would switch into Italian (his L2).

Evidently, the use of more than one language must alter the language network compared to that of a monolingual speaker of those languages, but it may also alter the network involved in its control. We suppose that language control recruits neural regions involved in the control of action in general (e.g., Green, 1986, 1998; see Pliatsikas & Luk, 2016, for a short review of the overlap of brain regions involved). The language network and the control network must also interact. Indeed, domain-general control processes operate in Broca's region classically held to be specialized for language (Fedorenko, Duncan, & Kanwisher, 2012; Snyder et al., 2010). Such interpenetration undermines the notion that any linguistically relevant region is encapsulated in the sense of Fodor (Fedorenko & Thompson-Schill, 2014) and may prove to be the norm in all regions comprising the language network. Indeed, as will be seen, we identify common regions. Granted the distinction between the language network and its control, we distinguish between the demand on the language network and the demand on the control network. Interpreting adaptive changes requires us to consider both types of demand. In order to do so, we need to consider our second question.

Neural Response to Increased Demand

What kinds of changes in the neural substrates might be expected in the light of increased demand? Responding to increased demand may lead to an increase in network efficiency or in the patterns of connectivity. Increased neural resources may be allocated to perform the neurocomputations required. Indeed, radically distinct regions might become recruited. However, it is surely more plausible that regions and networks specialized for the processing of lexical, syntactic, and prosodic information for one language are recruited to process information of the same type in a person's other language (see Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24 in this volume). There should be neural convergence (e.g., Consonni et al., 2013; Green, 2003). Adaptive change might then be detected in structural properties of the tissue (e.g., gray matter density). Within these common regions, neural representations for each language should be interleaved so that bilinguals can selectively use one language rather than another (Green, 2008; Paradis, 2004). However, on this issue of neural convergence, opinion diverges. Some researchers acknowledge convergence only for vocabulary, but not for syntax. We present evidence in later sections that supports neural convergence.

The Language-Control Network

Language-control processes are critical to both monolingual (e.g., Snyder et al., 2010) and bilingual speakers. Behavioral and event-related potential (ERP) studies (see Leckey & Federmeier, Chapter 3 in this volume) suggest that in bilingual speakers the two languages compete to control output (see Kroll, Dussias, Bice, & Perrotti, 2015, for a review). Control processes are needed for a range of purposes (Green & Abutalebi, 2013), for example to implement the intention to speak in one language rather than another, to monitor and regulate interference from the nontarget language (Abutalebi & Green, 2007; Costa, Miozzo, & Caramazza, 1999), though not to the same extent when the other language is a sign language (Emmorey, Giezen, & Gollan, 2016; see Corina & Lawyer, Chapter 16 in this volume). Control processes are also needed to disengage from using one language and to engage in using the other, or to code-switch between different languages within a conversational turn. Research has identified a network of cortical, subcortical, and cerebellar regions that orchestrate these processes and has identified some of their functions, but has yet to reveal details of the temporal dynamics that their orchestration requires. The primary regions involved are the dorsal anterior cingulate cortex (dACC)/pre-supplementary motor (pre-SMA) area, the left prefrontal cortex, the left caudate, and the inferior parietal lobules bilaterally (Abutalebi & Green, 2007), together with control input from the right prefrontal cortex, the thalamus and the putamen of the basal ganglia, and the cerebellum (Abutalebi & Green, 2016; Green & Abutalebi, 2013). We offer a selective review of the functions of each of these regions in the following section.

The dACC/pre-SMA Complex

ACC (anterior cingulate cortex) activity is usually related to conflict and error monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001) and activates during cross-linguistic conflict (Rodriguez-Fornells et al., 2005; van Heuven, Schriefers, Dijkstra, & Hagoort, 2008) and language switching (e.g., Guo, Liu, Misra, & Kroll, 2011; Hosoda, Hanakawa, Nariai, Ohno, & Honda, 2012; Luk, Green, Abutalebi, & Grady, 2012). Activation also increases when a relatively proficient L2 is re-engaged after a period of L1 immersion (Tu et al., 2015). It increases too when naming pictures in L2 after naming in L1 (e.g., Branzi, Della Rosa, Canini, Costa, & Abutalebi, 2015). In both cases, there is an increased need to monitor potential responses before overt speech. The increased demands in bilingual compared to monolingual speakers appear to tune its responsiveness to nonlinguistic conflict. Bilinguals, as compared to monolinguals, displayed reduced interference on a nonverbal flanker task (Abutalebi et al., 2012). Structurally, their performance correlated with increased gray matter density in the dorsal ACC, and functionally, bilinguals displayed a more efficient use of this structure.

The Left Inferior and Right Frontal Gyri

In contrast to dACC/pre-SMA, the left inferior frontal gyrus (IFG) is involved in response selection rather than conflict monitoring. It is commonly activated in language switching (e.g., Hernandez, Martinez, & Kohnert, 2000; Hosoda et al., 2012; Lehtonen et al., 2005) and during word generation, picture naming, and verbal fluency (see Abutalebi & Green, 2007), especially when producing words in the weaker language (De Bleser et al., 2003; Kovelman, Baker, & Pettito, 2008; Marian, Spivey, & Hirsch, 2003; Parker-Jones et al., 2012; Perani et al., 2003). In contrast with the response selection processes of the left IFG, the right prefrontal cortex appears to be associated with domain-general inhibitory control (Aron, Robbins, & Poldrack, 2014). Indeed, in the study by Branzi et al. (2015), switching back into L1 after naming in L2 induced increased activation consistent with the need to release inhibition of the dominant language. By contrast, they report significant deactivation for naming in L2 after naming in L1 (see Videsott et al., 2010, for a comparable pattern of response). Conceivably, increased additional demand on these regions for bilingual speakers may account for the greater cortical thickness in bilateral inferior frontal regions for these speakers (Klein, Mok, Chen, & Watkins, 2014).

The Inferior Parietal Lobules

The inferior parietal lobules comprise two distinct gyri: the supramarginal gyrus and the angular gyrus. We know that a posterior region of the supramarginal gyrus is responsive to vocabulary knowledge in monolingual and bilingual speakers (e.g., Lee et al., 2007; Mechelli et al., 2004). This region appears ideally placed to represent vocabulary, as it is connected to an anterior parietal region that processes phonology and the angular gyrus that processes meaning. We consider the representation and processing of vocabulary in more detail in a later section.

Inferior parietal lobules are also recruited in the context of attentional tasks, both in orienting attention in a voluntary manner and in responding to stimulus changes (Majerus et al., 2010; Shomstein, 2012). We should expect their involvement in language switching, and indeed both clinical (e.g., Pötzl, 1925) and functional neuroimaging data (e.g., Price, Green, & von Studnitz, 1999) confirm their involvement, but their coordination with other regions involved in language switching remains an open question.

Subcortical Structures: The Left Caudate, Putamen, and Thalamus

Green and Abutalebi (2013) postulated that a circuit involved in the detection of salient cues (e.g., Aron, Behrens, Smith, Frank, & Poldrack, 2007) would be important in ensuring sensitivity to the language context and in initiating a change in language. Neural circuitry would support such a role. Regions in the right inferior frontal cortex connect to the thalamus, which in turn connects two subcortical regions involved in language control: the left head of caudate and the putamen (e.g., Smith, Surmeier, Redgrave, & Kimura, 2011). The thalamus plays a role in shifting attention and action selection and connects to anterior and posterior regions of the left IFG (Ford et al., 2013). We suppose, then, that it is likely to play an important role in language production in bilingual speakers by aiding the selection of intended lexical and semantic representations, especially in the weaker or less exposed language in highly proficient bilingual speakers (see Consonni et al., 2013, for support).

Language switching and selection in production or in comprehension elicits activity in the left caudate (e.g., Abutalebi et al., 2007; Crinion et al., 2006; Lehtonen et al., 2005; Price et al., 1999) and lesions to the left caudate can induce a breakdown in language control (e.g., Gil Robles et al., 2005; Green & Abutalebi, 2008, for review). In contrast to dACC/pre-SMA activation, activation in the left caudate is contingent on language proficiency, with increased activation associated with a switch to the least proficient language (Abutalebi et al., 2013a). Such an outcome is consistent with a more general role of the left caudate in the control of action, where it is most active in overcoming habitual action plans (Ali, Green, Kherif, Devlin, & Price, 2010; Shadmehr & Holcomb, 1999).

Left putamen activity may reflect control of articulatory processes. In monolingual speakers (see Oberhuber et al., 2013), the left putamen is involved in overt speech production, with the anterior region involved in initiating novel articulatory sequences (as in the production of pseudo-words) and a posterior region associated with known or memory-guided sequences (producing words). The putamen is therefore likely to be sensitive to the articulatory demands of a second language. Indeed, Burgaleta, Sanjuán, Ventura-Campos, Sebastián-Gallés, and Ávila (2016) report volumetric increases in this structure, along with the thalamus, in simultaneous bilinguals compared to monolingual speakers (see also Abutalebi et al., 2013b). Its activation is also likely to be modulated by the demands for language control. In simultaneous interpreting, for instance, speakers must avoid articulating words they hear while producing words in the target language. In this circumstance, putamen activation varies with the duration of the overlap between listening and speaking (Hervais-Adelman, Moser-Mercer, Michel, & Golestani, 2015).

The Cerebellum

We supposed earlier that language control recruits structures involved in the control of action in general. The cerebellum is a further critical structure. It is linked to all the key regions of the language-control network (Green & Abutalebi, 2013), including the right inferior frontal cortex, which, as we noted, is connected via the thalamus to caudate and putamen regions of the basal ganglia. Research has established its contribution to a wide range of language and cognitive functions in addition to motor processes (see Tyson, Lantrip, & Roth, 2014, for a review). For example, the right cerebellum forms a circuit with the left inferior frontal cortex (Krienen & Buckner, 2009). Clinical data indicate that such a circuit supports morphosyntactic processing: lack of right cerebellar activation impaired speech production in bilingual speakers (Marien, Engelborghs, Fabbro, & De Deyn, 2001; Silveri, Leggio, & Molinari, 1994).

THE LANGUAGE NETWORK

What are the neural substrates of the language network? On a classical view, the language network comprises a set of regions in left frontal and temporal cortices together with the inferior parietal cortex. Multiple long-range white matter fiber bundles (pathways) interconnect these regions. Together, they are held to support language production and comprehension (Vigneau et al., 2006). Most interestingly, distinct dorsal and ventral pathways seem to support the syntactic, semantic, and sensorimotor processes required in language use (Friederici, 2015), though precisely how these pathways work together to integrate sound, syntax, and meaning in speech production is underdetermined. We can, though, make use of the functional dissociations implied.

They allow us to determine whether the neural signatures for processing vocabulary or processing syntax in a second language are the same or different from those identified in the first language; accordingly, we describe them briefly.

Broadly speaking, regions in the dorsal pathways mediate sensorimotor and syntactic processes, whereas those in ventral pathways mediate semantic processing. The dorsal pathway from the temporal cortex via the inferior parietal area to the premotor cortex (the superior longitudinal fasciculus) supports sensory to motor processing, as in speech repetition (Hickok & Poeppel, 2007; Saur et al., 2008). A second dorsal pathway (the arcuate fasciculus; Wernicke, 1874), which directly connects the pars opercularis (BA 44 of Broca's area) and Wernicke's area, appears necessary to the processing of syntactically complex sentences (Wilson et al., 2011). The pars opercularis may support such processing because it is involved in phonemic discrimination and phonological rehearsal and so may act to retain the wording of the sentence. Phonological rehearsal may be critical, too, in the learning of new vocabulary. Undoubtedly, other dorsal pathways are likely to support speech production. For example, the frontal aslant tract connecting the pars opercularis to the superior frontal regions (Catani et al., 2012) may support speech planning and initiation (Dick, Bernal, & Tremblay, 2014).

Of the designated ventral pathways, one supports semantic processing through its linking of BA 45, the pars triangularis in Broca's area and BA 47, to occipito-temporo-parietal regions, via the extreme capsule fiber system (the longitudinal inferior-fronto-occipital fasciculus). A second pathway (the uncinate fasciculus) connects the anterior temporal cortex (a region viewed as a conceptual hub) and the orbitofrontal cortex. It serves to integrate the meaning of lexical concepts (e.g., cherry-cake vs. bread-cake; Feng, Chen, Zhu, & Wang, 2016) and so may complement the dorsal pathway for syntax by processing local phrase structure (e.g., Friederici, 2015; Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013).

This view of the language network is noticeably cortico-centric, but subcortical and cerebellar regions are also pertinent to language comprehension and production (see Price, 2012, for an overview of the regions involved). Recent work provides good evidence of connections between regions in Broca's area and basal ganglia structures (Ford et al., 2013; Kotz, Anwander, Axer, & Knösche, 2013), also via the insula (Oh, Duerden, & Wang, 2014), and between the left inferior frontal cortex and the right cerebellum (Krienen & Buckner, 2009; see also Tyson et al., 2014). Basal ganglia structures are likely to be integral to sentence formation.

On one proposal, consistent with the multiple reciprocal connections between the frontal cortex and the basal ganglia, control signals serve to update, maintain, or output the constructed sentence plan (Kriete, Noelle, Cohen, & O'Reilly, 2013). For bilingual speakers, language-control signals will be needed to select a relevant structure in the intended language and to select among competing items that may be from both languages (see also Stocco, Yamasaki, Natalenko, & Prat, 2014, for a related view).

Distinct activation profiles have been identified during sentence production for two basal ganglia structures: the putamen and the caudate. The putamen contributes to articulation (together with cortical areas such as the pars opercularis) during both sentence repetition and sentence generation, whereas the caudate supports the process of selecting sentence structure and form during sentence generation (Argyropoulos, Tremblay, & Small, 2013). We know of no comparable published study with bilingual speakers that allocates a functional role to these two structures during sentence generation. However, interesting data from a simultaneous interpretation task support the role of the caudate in language selection and indicate the sensitivity of the putamen to increased articulatory demand (Hervais-Adelman et al., 2015). In other research, increased articulatory demand during sentence generation in a less proficient L2 also increases functional connectivity of the left putamen with the left pars opercularis (Dodel et al., 2005).

Interestingly, both the pars opercularis, implicated in phonology and syntax, and the pars triangularis, implicated in semantic processing, are connected to the anterior putamen. Ford et al. (2013) proposed that this arrangement ensures that the intended semantic response is articulated with appropriate phonemes. Overall, the fronto-subcortical circuits (along with thalamic input) may serve to sharpen and fine-tune output during lexical selection, with the caudate actively involved in selecting the relevant linguistic structure. These regions and circuits should be sensitive to the demands of bilingual speech.

Cerebellar regions also play an important role in both overt speech (e.g., verbal fluency) and inner speech (Tyson et al., 2014). In the case of verbal fluency, gray matter density in bilateral inferior cerebellar regions correlated with the number of words produced during letter and semantic fluency tasks for both L1 and L2 (Grogan et al., 2009). In line with the role of the cerebellum in sentence processing, gray matter cerebellar volume, though not specifically right cerebellar volume, correlated with efficient processing of L2 morphosyntax in immersed, proficient L2 speakers (Pliatsikas, Johnstone, & Marinis, 2014).

Functional imaging studies using sentence production and comprehension tasks have yet to elucidate the set of cerebellar contributions to language processing, but one general function may be predictive (Ito, 2006). Repetitive transcranial magnetic stimulation applied to the right cerebellum delays eye movements to a target object predicted by sentence content (Lesage et al., 2012). Cerebellar regions may also aid in maintaining an ongoing representation of a sentence during comprehension or in resolving conflicting inputs. In line with the latter possibility, gray matter density in a region of the right cerebellum predicts resistance to speech interference as bilingual speakers comprehend an utterance in their second language while listening to speech in their first language (Filippi et al., 2011). A re-analysis of data in Crinion et al. (2006) with this area as a region of interest confirmed that it was most active when resisting interference from L1. Such an outcome supports the notion that functional demand may underlie structural response. We also note that the same region responds to language conflict in monolingual English speakers (e.g., when silently reading words with irregular spellings; Osipowicz et al., 2011), indicating that it is not specialized for language control in bilingual speakers. It provides a further example of neural convergence.

ADAPTIVE CHANGES IN THE LANGUAGE AND CONTROL NETWORKS

Basic differences between languages provide a potential trigger for adaptive change. A study by Krizman, Marian, Shook, Skoe, and Kraus (2012) provides an excellent illustration. In a multi-speaker context, bilinguals must be able to select the relevant target language and adjust their own speech. Fundamental pitch (F0) provides a cue for identifying the language of use and is encoded in the auditory brainstem. Given its functional relevance, Krizman et al. (2012) reasoned that bilinguals might attend to this cue and amplify its neural representation. In line with expectation, relative to monolingual English speakers, bilingual speakers showed enhanced auditory brainstem responses to changes in fundamental pitch. Most interestingly, given our interest in the language network and in its control, they also showed enhanced performance on a test of sustained attention, with performance correlating strongly with brainstem response in the multi-talker context. A language demand, then, can induce a strong coupling between an attentional process and the physiological encoding of a relevant auditory cue.

Bilinguals must be able to not only discriminate the relevant auditory cues, but also process and represent the words of the languages in order to derive the meaning of an utterance and its significance. Auditory cortex is clearly implicated, and so it is fair to ask if there is evidence that the learning and lifelong use of two languages affects it in any way. Given that musical training can lead to an increase in its volume (e.g., Schneider et al., 2002), does the learning and use of more than one language yield an auditory expertise effect? A study examining the volume of Heschl's gyrus (HG) showed greater volume in young Catalan-Spanish students compared to their age-matched monolingual Spanish controls consistent with the notion that bilingual experience (at least when both languages are learned simultaneously at an early age) does indeed cause changes in this region of the auditory cortex (Ressel et al., 2012).

Other research suggests that the specific auditory properties of a language can exert an effect. For example, Mandarin uses tone to mark lexical differences, and so regions associated with the processing of pitch might be expected to differ between Chinese and non-Chinese speakers, regardless of ethnicity differences. In one voxel-based morphometry study, native Chinese speakers and Europeans who had learned Chinese as a second language showed increased gray and white matter in the right temporal pole and left insula compared to monolingual English speakers or bilingual speakers who spoke no Chinese (Crinion et al., 2009).

The Representation and Processing of Vocabulary

Knowledge of words, their senses, referents, sounds, and written forms is distributed over many regions of the brain. We consider the implications for bilingual lexical processing, for acquiring vocabulary knowledge, and for speaking words in two languages.

Lexical Access

Initial evidence for the idea that there are interleaved representations within common areas comes from intra-operative cortical stimulation studies (see Duffau, Chapter 8 in this volume) that identify sites where speech arrest arises for one language but not another (Lucas, McKhann, & Ojemann, 2004; Ojemann & Whitaker, 1978; Roux & Trémoulet, 2002). Such results do not imply localization of an object name, but rather interruption of a naming circuit. Data better suited to address this question come from studies that examine patterns of neural response in the functional magnetic resonance imaging (fMRI) response to translation-equivalent words. In processing such words, we should expect to find two kinds of data: language-distinct patterns within common regions that reflect their distinct acoustic and phonological properties of the translation equivalents, and language-independent patterns that reflect the fact that such equivalents access modality-independent knowledge of the referents of those words.

Using multi-voxel pattern analyses, Correia et al. (2014) reported that discriminating neural response to individual spoken animal nouns (horse/duck) within each language (English/Dutch) involved multiple temporal, parietal, and frontal cortical regions. Some regions (such as the left anterior temporal lobe) revealed an invariant response pattern to the translation equivalents (paard/eend), indicative of access to common semantic/conceptual knowledge. The anterior temporal lobe also shows adaptation effects in cross-language semantic priming in reading single words from different categories (Crinion et al., 2006). The processing of verbs loads on a different set of regions (e.g., Tyler, Randall, & Stamatakis, 2008), but neuroimaging data confirm that the set of regions involved is identical in the two languages of proficient adult bilingual speakers (Consonni et al., 2013). Our expectation is that a multi-voxel pattern analysis would reveal a comparable interleaved pattern in the processing of verbs.

Further evidence for the tight neural coupling of translation equivalents comes from studies using ERPs to monitor the first moments when bilinguals process words in one language alone. Thierry and Wu (2007) asked Chinese-English bilinguals immersed in an English-dominant context to perform a semantic relatedness judgment on a pair of English words. Unbeknownst to these bilinguals, the two English words had translations in Chinese that sometimes shared the same characters. They found that bilinguals, but not monolingual speakers of English, showed a modulated N400 when there was a conflict between the semantic match of the English words and the form mismatch of the Chinese characters. Because no actual Chinese was present in the experiment, the result suggests that the Chinese translations of the English words were activated implicitly in the first few hundreds of milliseconds of processing the English as the L2. The result is particularly striking because the two languages do not share the same written script. Similar behavioral results have been reported for deaf readers in the United States who appear to activate translations in American Sign Language when they are reading English words (Morford, Wilkinson, Villock, Piñar, & Kroll, 2011). Three features of these results are critical to our discussion. One is that the co-activation of the bilingual's two languages does not depend on the similarity of word form. Form relations may modulate responses, but the very existence of the two languages is what appears to be important. A second is that co-activation across the two languages happens quickly and without conscious intention. A third is that these interactions are not a reflection of early stages of learning, but characterize the performance of highly proficient bilingual speakers and readers.

Acquiring Vocabulary Knowledge

In order to access modality-independent knowledge through language, speakers need vocabulary. Current evidence favors the notion that temporal and parietal regions mediate key components of vocabulary knowledge. In monolingual speakers, inferior temporal regions are actively engaged in semantic fluency tasks, that is, in the paced retrieval of words from a specified semantic category (e.g., Mummery, Patterson, Hodges, & Wise, 1996). Bilingual speakers engage the same region, with gray matter density predictive of the relative performance in a semantic fluency compared to a phonemic fluency task in both L1 and L2 (Grogan, Green, Ali, Crinion, & Price, 2009).

Vocabulary knowledge as such is linked in monolingual adolescents to gray matter density in posterior regions of the supramarginal gyrus (pSMG) (Lee et al., 2007), whereas in adult monolinguals, vocabulary knowledge correlates with gray matter density in two left temporal regions associated with sentence processing (Richardson, Thomas, Filippi, Harth, & Price, 2009). In bilingual speakers, vocabulary knowledge appears to load on the pSMG. This region is not typically activated in phonological tasks but, as indicated earlier, it connects to an anterior region that does activate and to the angular gyrus activated in semantic tasks. It thus may serve as a region that integrates two sources of information fundamental to vocabulary: how a word sounds and its meaning. Indeed, Mechelli et al. (2004) reported higher gray matter density in pSMG in Italian-English bilinguals as compared to English monolinguals. Furthermore, gray matter density covaried positively with L2 proficiency and negatively with age of learning the L2 (see also Grogan et al., 2012).

Given the results of Lee et al. (2007), the correlation with proficiency is most plausibly attributed to an increase in L2 vocabulary knowledge (see Grogan et al., 2012, for an association with the number of languages spoken). Further corroboration comes from a longitudinal study in children by Della Rosa et al. (2013). A regional increase in gray matter density correlated with increased language proficiency over a one-year period. Abutalebi, Canini, Della Rosa, Green, and Weekes (2015a) confirmed the persistence of this correlational effect in older bilinguals. The persistence of the association over time may suggest a reduced reliance in bilingual speakers on sentence contexts to expand vocabulary, or a continued reliance on processes that served to expand vocabulary in the first place. Conceivably, there are individual differences within speakers such that those better able to induce meaning from context rely on more temporal regions, whereas those better at phonological processing rely on more parietal regions.

Individual differences in the structure of the regions associated with subvocal rehearsal (see Golestani & Pallier, 2007; Golestani, Molko, Dehaene, LeBihan, & Pallier, 2007) or in their functional connectivity (see Veroude, Norris, Shumskaya, Gullberg, & Indefrey, 2010; also Xiang et al., 2012) do appear to affect the ease with which individuals can learn novel words. In a short-term training study using lexical tone in a word-picture task, Yang, Gates, Molenaar, and Li (2015; see, earlier, Wong, Chandrasekaran, Garibaldi, & Wong, 2011) examined the causal structure of the network mediating successful word learning. In line with the importance of preexisting individual differences, successful learners displayed a better integrated fronto-temporo-parietal network (including SMG) before learning as well as after learning (see Li, Legault, & Litcofsky, 2014, for a more detailed review of such training studies). Individual differences in resting-state functional connectivity between frontal and temporal regions, and between frontal regions and dorsal ACC, also predict the efficiency of lexical retrieval following an intensive French immersion course (Chai et al., 2016). Such data suggest that neural signatures can be used to predict the ease with which adults can learn a new language.

Subcortical structures are also likely to play an important role in word learning and help explain individual differences in word learning. In the case of reading, for example, differential activation of the caudate-fusiform circuit is predictive of changes in reading skill (see Tan et al., 2011). Reward circuits may also be critical. Subcortical areas mediating reward, such as the ventral striatum, are activated by a range of rewarding stimuli covering food, money, and artistic or intellectual pleasures. It is plausible that language learning (see Syal & Finlay, 2011) recruits the same areas. A number of interrelated predictions arising from this proposal were tested in a study examining the neural substrates for learning the meanings of novel words (Ripollés et al., 2014). The study showed that the ventral striatal region involved in correctly learning the meaning of new words was active in a task involving monetary gains and so established a tight coupling between correctly learning the meaning of a new word and the modulation of a phylogenetically older system involved in reinforcement learning.

More specifically, the study established that activation in the ventral striatum increased for new words that were learned, and that such learning also increased activation in cortical regions of the language network (left IFG, left middle temporal lobe, left inferior parietal gyrus; the left hippocampus was also active). If reward signals drive regions in the language network, then there should be increased connectivity between ventral striatum and pertinent regions in the language and control network. In line with expectation, functional connectivity analysis confirmed that learning increased the coupling of left ventral striatal activation with activation in regions in the left IFG (pars opercularis [BA 44], pars triangularis [BA 45], and BA 47), the supplementary motor area, and the left caudate. A further analysis nicely showed that the percentage of success in learning new words was related to the integrity of the white matter pathways reaching the ventral striatum, as well as pathways in the language network (inferior fronto-occipital fasciculus associated with semantic processing and the left uncinate fasciculus, linking the anterior temporal pole and the orbitofrontal cortex). Overall, these functional and anatomical data cohere to support the role of subcortical reward-related areas, together with regions and pathways in the language network, in predicting the success with which individuals learn the meanings of new words.

Spoken Lexical Production

Adaptive changes to the language network can also be seen in the performance of highly proficient bilinguals. Studies that characterize skilled bilingualism are important not only because they enable us to identify the scope of language plasticity, but also because they demonstrate that skilled bilinguals are not monolingual native speakers in either of their two languages, a point made many years ago by Grosjean (1989). A theme in recent studies of bilingual lexical production is that the native language is continually regulated, presumably to engage those control mechanisms that eventually allow for fluent performance in the weaker language and to coordinate the use of the two languages in different contexts (e.g., Green & Abutalebi, 2013). What has become evident is that this coordination is not a simple effect, but depends on the level of resource demands associated with particular task goals.

A second language increases the articulatory repertoire involved in producing words. Given monolingual data on the involvement of the anterior putamen in producing less familiar forms (nonwords; Oberhuber et al., 2013; see earlier discussion in the chapter), we should expect the functional activation of this region during naming in L2 to reduce with proficiency, and this seems to be the case (Abutalebi et al., 2013b). Other frontal regions are known to be sensitive to lexical demands in monolingual speakers. The left IFG is implicated in the paced retrieval of words (e.g., Thompson-Schill, D'Esposito, & Dan, 1999). Bilingual speakers, at least in their L2, need to resolve lexical competition with L1, and the left pars opercularis in the left IFG shows such an effect (Parker-Jones et al., 2012). If structural change follows functional demand, then we may predict that the speed and accuracy with which bilingual speakers recognize and produce words in their L2 (lexical efficiency) should correlate positively with gray matter density in this region, and it does (Grogan et al., 2012; see also Stein et al., 2012). The precise nature of the lexical demand detected here is not resolved, but it is noteworthy that structural differences in this region (along with others in auditory and parietal regions) are predictive of individual differences in the ease of perceiving and producing foreign speech sounds (Golestani & Pallier, 2007; Golestani, Molko, Dehaene, LeBihan,

& Pallier, 2007). Such data are consistent with the role of the left pars opercularis in phonemic processing and subvocal rehearsal in working memory (e.g., Gough, Nobre, & Devlin, 2005).

A comparison of phonemic and semantic fluency in bilingual speakers reveals further regional correlations with gray matter density. Gray matter density in the head of caudate bilaterally predicted relative performance for the phonemic over the semantic fluency task, particularly in L2 (Grogan et al., 2009) This outcome is consistent with the idea that the caudate helps to control interference from prepotent responses (e.g., L1) or to assemble phonemes into words as part of a procedural system (Ullman, 2001)—a task that would be more effortful for the L2. Gray matter density in bilateral pre-SMA also predicted relative phonemic over semantic fluency performance. This region is associated with the planning and preparation of movement (e.g., Petrides, Alivisatos, Meyer, & Evans, 1993) but surprisingly, there was no differential effect of language in this region, where one might have expected the correlation to reflect the increased monitoring demands for L2.

Recent studies also have examined the carryover effects of prior use of one language on lexical production in the other (see Kroll & Gollan, 2014, and Kroll, Gullifer, McClain, Rossi, & Martín, 2015, for recent reviews). In brief, the evidence suggests that when bilinguals are required to speak their native or dominant L1 following speaking the weaker or less dominant L2, there is inhibition of the L1. The need to select one language alone requires the engagement of resources to reduce the activation of the more available alternative. The consequence of speaking the L2 for the L1 can be seen in ERP data (e.g., Branzi, Martin, Abutalebi, & Costa, 2014; Misra, Guo, Bobb, & Kroll, 2012), in behavior (Van Assche, Duyck, & Gollan, 2013), and in fMRI data (e.g., Branzi et al., 2015; Guo et al., 2011). The modulation of the L1 in the face of demands to speak the L2 suggests that bilinguals acquire skill in language regulation. What is notable in the studies mentioned is that the requirement to regulate the more dominant language is not simply a momentary event that is observed when bilinguals switch from one language to the other in forced trial-to-trial switching paradigms (e.g., Meuter & Allport, 1999). Rather, it occurs even when bilinguals have an opportunity to speak in the L1 for an extended period of time, suggesting that there are sustained inhibitory control mechanisms that may have the consequence of suppressing the non-target language globally. A focus in recent studies is to identify the mechanisms that may contribute to inhibitory control in different circumstances, with some hypothesized to operate more locally, for specific lexical alternatives and perhaps with short-term consequences, and others that may operate more globally, with respect to both scope and time course.

It is of interest to note that a series of studies has asked about the consequences for cognitive control when these selection demands are absent in production. For hearing individuals who use a signed language, there is the possibility of co-gesturing while speaking. Therefore, a choice along the same output channel is not required. Both behavioral (Emmorey, Luk, Pyers, & Bialystok, 2008) and structural imaging data (Olulade et al., 2015) on bimodal bilinguals support the claim that the ease of selecting the language to be produced is one source of the observed consequences of bilingualism. In the absence of a high selection demand, neither behavioral advantages nor structural changes in the brain were observed for bimodal bilinguals relative to their unimodal counterparts. The precise contexts of bimodal language use may be important; Zou, Ding, Abutalebi, Shu, and Peng (2012) report increased gray matter volume of head of caudate, relative to monolingual speakers, for late learners of Chinese sign language who were teachers of it. In this sample, conceivably because of the teaching context, selection demand may be high. Indeed, activation of the left head of caudate was associated with language switching consistent with the role of the left caudate in the selection of competing action plans.

Representation and Processing of Syntax in the Bilingual Brain

Where scientific opinion, at least until recently, has been most strongly divided is whether or not the learning of a second language necessarily leads to a difference in the representation of syntax. Post-stroke, languages tend to recover in line with their relative premorbid proficiency (e.g., Paradis, 2004), but some neuropsychological case reports do associate distinct lesion sites with the selective recovery of L1 or L2 (e.g., García-Caballero et al., 2007; see also Aladdin, Snyder, & Ahmed, 2008). However, such selective recovery may also be the result of damage to circuits involved in language selection, and so we do not consider such evidence decisive.

Why might L2 syntax be represented in a different fashion, at least at low levels of L2 proficiency (Paradis, 2004, 2008; Ullman, 2001)? The argument here is that syntax is acquired implicitly for L1 and is represented in subcortical regions of the basal ganglia that contribute to procedural or skill-based memory. By contrast, L2 grammatical rules are learned explicitly and are represented declaratively in cortical regions. Stroke may then yield different effects in L2 because subcortical damage, for instance, will leave the declarative representations of L2 to drive processing, whereas these will not be available to drive processing in L1. Much larger samples of patients with subcortical lesions are needed to test this idea, but current lesion-deficit data favor common representations for L1 and L2. In an analysis of the lesion-deficit associations involving a wide battery of language skills, including those requiring syntactic processing, Hope et al. (2015) found that monolingual and bilingual patients were sensitive to damage in the same sets of regions, though bilingual patients showed greater sensitivity to damage, perhaps reflecting their lower premorbid proficiency. fMRI data also indicate the involvement of cortical, subcortical, and cerebellar regions in common with those activated in monolingual speakers, when bilingual speakers read sentences aloud either in their native or in their non-native language (Berken et al., 2015).

If neural convergence holds, ERP, magnetoencephalography (MEG), and functional imaging data should provide evidence that L2 learners engage in native-like syntactic processing at the very earliest stages of L2 learning.

NATIVE-LIKE PROCESSING OF L2 SYNTAX AT THE EARLIEST STAGES OF L2 LEARNING

Longitudinal studies of beginning learners of a language provide critical evidence for the way in which an L2 grammar is learned. Neurocomputationally, convergence with native-speaker profiles of processing L2 syntax should operate at relatively early stages of L2 learning. That assumption is contrary to the traditional claim that the syntax is inaccessible to late L2 learners, leading them to adopt alternative means to achieve comprehension (e.g., Clahsen & Felser, 2006), by using semantic or pragmatic information to circumvent the syntax itself. In fact, the neurocognitive evidence provides strong support for the proposal that most features of the syntax and morphosyntax are available to late L2 learners, although some may require greater adjustment than others as learning proceeds (see Roncaglia-Denissen & Kotz, 2016, for an overview). The approach that has been most revealing in identifying the nature of processing the syntax in the L2 has been the use of ERPs. ERPs provide a temporally sensitive window into the first moments of sentence processing as they occur online. If bilinguals who have acquired the L2 past early childhood are required to adopt different strategies to process the grammar than those used by native speakers, then the ERP record would be expected to reveal those differences. As we will see, recent ERP data provide evidence for much greater adult plasticity with respect to syntax than previously assumed by the traditional view (see Duñabeitia, Dimitropoulou, Dowens, Molinaro, & Martin, 2016, and Van Hell & Tokowicz, 2010, for reviews on ERPs and language processing).

Two early studies using ERPs to investigate the role of age of acquisition (AoA) for sensitivity to L2 syntax initially appeared to support the traditional claims about critical periods in language learning (Hahne & Friederici, 2001; Weber-Fox & Neville, 1996). These studies adopted the logic of the classic behavioral study reported by Johnson and Newport (1989) in which late learners were more likely than native speakers to make errors in judging the grammaticality of sentences. The initial ERP data seemed to bolster this claim by demonstrating that in the presence of syntactic violations, late L2 learners did not appear to produce the signature ERP effects that have been observed for native speakers, an LAN effect (left anterior negativity) and a P600. Since these reports, there has been a stream of criticism centering around methodological issues and, critically, the observation that AoA is confounded with L2 proficiency (e.g., Steinhauer, 2014). Although all would agree that there are consequences of age of exposure that may be reflected in brain structure and function (e.g., Klein, Mok, Chen, & Watkins, 2014), those consequences may not present hard constraints in acquiring sensitivity to the L2 grammar.

Subsequent studies have taken two different approaches to examine features of the syntax. One is to ask whether highly proficient but late L2 learners process the syntax and morphosyntax like native speakers. The other is to examine neural response to the learning of artificial grammar or to use longitudinal methods to track the developmental trajectory of adult L2 learners during the earliest stages of learning. fMRI data of neural response to the processing of syntactic structures from an artificial grammar indicate commonality with the neural substrate mediating syntactic processing in a natural language. For example, the arcuate fasciculus, with its direct connection between BA 44 and the temporal cortex, underlay the processing of novel syntactic structures in a comprehension task (Friederici, Bahlman, Heim, Schubotz, & Anwander, 2006) identical to the pathway required in the processing of complex structures in a natural language (Wilson et al., 2011). Learning novel syntactic structures also elicited an identical profile in MEG responses to syntactic structures in English (Ding, Mellon, Zhang, Tian, & Poeppel, 2016).

More germane to the bilingual case, Morgan-Short, Steinhauer, Sanz, and Ullman (2012) used an artificial language under conditions of implicit or explicit training to ask whether learners can acquire native-like responses to syntactic violations. They compared the two types of training for learners who had become proficient in the artificial language or not. The two types of training were taken to be a model of immersion (implicit) versus classroom (explicit) learning conditions. Although the two learning groups at the two levels of proficiency did not differ in behavioral measures, the ERP record revealed clear consequences of both factors. Individuals who had learned implicitly and had achieved a relatively high level of proficiency in the new language produced an ERP pattern that has been associated with native-speaker responses to syntactic violations; there was an anterior negativity, followed by a P600 and a late anterior negativity. Individuals who had become relatively proficient following explicit training did not reveal the late anterior negativity, suggesting that implicit learning may enable native-like performance, even following relatively brief exposure to the new language. In a follow-up study, Morgan-Short, Finger, Grey, and Ullman (2012) compared relatively high-proficiency learners in this paradigm after they had a period of 3–6 months with no exposure to the language. Contrary to the expectation that attrition would be observed, upon retesting they found that both implicit and explicit learners produced a pattern of ERPs that was more native-like than the initial test, although the implicit learners maintained a native-like profile relative to the explicit learners. Beyond the nuances of learning method, the significance of these findings is that they demonstrate, first, that it is possible for adult learners to acquire sensitivity to the syntax following relatively brief exposure, and second, that ERPs may reveal learning prior to behavior (see Tokowicz & MacWhinney, 2005, for a similar claim).

An ideal approach to investigate the trajectory of new learning is to track learners longitudinally as they become more proficient in the L2. The pragmatic constraints required by longitudinal designs make these studies difficult to carry out, but there are a number that have used ERPs to assess the presence and changes in L2 learning over time. McLaughlin, Osterhout, and Kim (2004) first examined word learning in a group of college students learning French as a foreign language. Quite remarkably, they demonstrated that after only 14 hours of classroom exposure, the ERPs to discriminate words and nonwords began to reveal recognition of the new French vocabulary, as indexed by an N400. In contrast, behavioral measures of recognition remained at chance at this early stage of learning, suggesting that the brain is beginning to register new learning before it is manifest in behavior. Using the same approach, with just a month of instruction, Osterhout et al. (2008) showed that at least some learners were able to discriminate between sentences that were well formed and those that contained a syntactic violation. However, unlike native speakers, the learners initially produced an N400 to those violations rather than a P600. After four months of L2 instruction, the N400 was replaced by a P600, suggesting a developmental trajectory with changes occurring very early in learning, although only for some learners and for some structures (and see McLaughlin et al., 2010). Related studies have begun to examine individual differences in sensitivity to syntactic violations and in the trajectory of new language learning (e.g., Tanner, McLaughlin, Herschensohn, & Osterhout, 2013). Although there is a great deal that is yet unknown about the factors that contribute to the developmental course of new L2 learning or the individual differences that modulate the trajectory of learning, the general implications are clear. Obstacles to complete acquisition of the L2 syntax reflect aspects of the learner and the learning context, rather than a set of hard constraints. Critically, the neurolinguistic evidence reveals a system that is more open to new learning and to even subtle aspects of the syntax than previously understood and also is more plastic during even the very first moments of exposure to the second language.

NATIVE-LIKE PROCESSING OF L2 SYNTAX FOR HIGHLY PROFICIENT LATE BILINGUALS

The approach taken by Morgan-Short and colleagues, and others, in using an artificial language learning paradigm can be criticized on the grounds that artificial language learning necessarily involves a smaller number of tokens and structures that may overestimate the ability of adult learners. Thus, an important question is whether similar patterns can be seen in studies with actual languages with relatively proficient L2 speakers who acquired the L2 as adults. There are many studies that have taken this approach, and although the evidence is complex, with varied findings across different types of structures and speakers, there is general support for the notion that late L2 learners who are able to become highly skilled reveal similar patterns of sentence processing relative to native speakers of the language (e.g., Bowden, Steinhauer, Sanz, & Ullman, 2013, and see Steinhauer, 2014, for a review of the recent studies; and earlier section of this chapter for fMRI data).

A number of factors may determine the ability of late bilinguals to achieve native-like status, including structural differences across the two languages and individual differences among L2 learners. The exercise becomes more complex when one considers that even for the most proficient bilinguals, the ease of activating particular syntactic structures may be influenced by cross-language processing. While bilinguals may activate the syntax of both languages in parallel (Sanoudaki & Thierry, 2015), there also may be constraints imposed when structures within each language are incongruent. For example, Hartsuiker, Pickering, and Veltkamp (2004) used a syntactic priming paradigm behaviorally to demonstrate that it was possible to observe priming across languages when structures are shared. Other studies have shown that when the languages diverge, for example, in their reliance on word order, then priming is typically not found (e.g., Bernolet, Hartsuiker, & Pickering, 2007; Loebell & Bock, 2004). The ability to acquire sensitivity to the L2 syntax does not mean that all structures are necessarily processed in parallel (but see Vaughan-Evans, Kuipers, Thierry, & Jones, 2014, for some ERP evidence to the contrary). Likewise, not all learners may reveal the same trajectory of learning or adopt the same strategies to process all structures. A number of recent ERP studies have shown striking individual differences in patterns of ERP sentence processing for both monolinguals and bilinguals (e.g., Pakulak & Neville, 2010; Tanner, Inoue, & Osterhout, 2014), suggesting that caution needs to be exercised when interpreting differences across groups.

In a recent review of the research using ERPs to assess L2 sensitivity to syntax, Caffarra, Molinaro, Davidson, and Carreiras (2015) analyzed the aggregated data from a large number of studies to ask which factors determine the presence or absence of sensitivity to syntactic violations. Their analysis suggested that both L2 proficiency and language immersion experience have consequences for late acquirers, but that each of these variables affected a different aspect of L2 processing, with early effects for immersion and later control or monitoring effects associated with proficiency. An interesting result in the Caffarra et al. paper was that there was no evidence within the limits of the analysis performed to suggest that the similarity between the L1 and L2 was critical.

Another logic that has been adopted to investigate these issues is to select features of the syntax or morphosyntax that are subtle and typically difficult to acquire. A long line of studies has investigated the acquisition of grammatical gender from this perspective to ask whether the acquisition of a gender-marked language is more difficult when the learner's native language also marks gender but differently than the L2, or does not mark gender at all, as is the case for English learners. Recent ERP studies have produced results that are somewhat mixed but generally suggest that late bilinguals are indeed able to acquire sensitivity to gender (e.g., Foucart & Frenck-Mestre, 2012; Meulman, Stowe, Sprenger, Bresser, & Schmid, 2014) and that knowledge and use of gender in one language may influence the other language even when it does not mark gender (e.g., Ganushchak, Verdonschot, & Schiller (2011). Rossi, Kroll, and Dussias (2014) took the approach of focusing on a subtle feature of Spanish to examine the ability of late English-Spanish bilinguals to process clitic pronouns. Clitics do not exist in English and are also marked for gender and number in Spanish. Rossi et al. found that relatively proficient late English-Spanish bilinguals were sensitive to violations of number marked on the clitic, resulting in a P600 in the ERP record, but were not sensitive to violations of gender. When proficiency was taken into consideration, the most proficient bilinguals among these late learners were indeed sensitive to violations of gender as well as number, suggesting that it is possible to acquire native-like ability to process structures that are unique to the L2.

The literature on the processing of syntax in two languages is only beginning to examine the neural basis of those aspects of language use that may be uniquely bilingual, such as intra-sentence code-switching. Some bilinguals code-switch with others similarly bilingual in the middle of a sentence, and the linguistic data demonstrate that these switches are far from arbitrary in that they follow constraints that appear to be imposed by grammar and by the relationship between production and comprehension (e.g., Guzzardo Tamargo, Valdés Kroff, & Dussias, 2016). Understanding the neural control of code-switching will be an important direction for future research on the syntax (see Green & Wei, 2016, for a discussion of code-switching and language control). Other studies show that the L1 grammar comes to be influenced by the L2, again revealing a level of plasticity that might not have traditionally been expected (e.g., Dussias & Sagarra, 2007). The neural basis of these bilingual phenomena are not yet well understood but will be important in shaping the next stages of research. They are compatible with imaging data that suggest that the same neural tissue supports both languages. The effects of the L2 on the L1 are of additional interest in light of discussions of acquiring native-speaker facility in an L2. If proficient bilinguals change the way they process the native language as a consequence of the active use of a second language, then the native-language model may be that of a bilingual rather than monolingual speaker.

Neural Plasticity and Neural Reserve

In the introduction to this chapter, we referenced studies on cognitive decline and reported diagnosis of Alzheimer's disease that point to the potential neuroprotective role of lifelong bilingualism. Neuroprotective effects plausibly derive from the adaptive changes required to represent and use two languages. To the extent that everyday language use involves distinguishable demands on the control and language networks, then the cumulative effects will be realized in structural changes in the regions most affected and in the networks that interconnect them. In addition to the changes in specific regions noted in earlier sections, there are reports of widespread neural difference in the brains of young adults who are bilingual rather than monolingual. For instance, Burgaleta et al. (2016) reported bilateral gray matter volumetric differences in inferior frontal, inferior temporal, parietal, and cerebellar regions, in addition to the volume differences in the putamen already discussed. By contrast, they noted increased volumes for monolinguals in the left middle and superior temporal gyrus, arguably consistent with the adult monolingual vocabulary data of Richardson et al. (2009). At the network level, García-Pentón, Perez, Iturria-Medina, Gillon-Dowens, and Carreiras (2014) identified two networks with increased connectivity in bilinguals compared to monolinguals: one comprising left hemisphere language-related and language-control regions and the other arguably more linked to semantic processing but including a frontal control region (see also Berken, Chai, Chen, Gracco, & Klein, 2016). Such data argue for profound neural differences arising from the experience of learning and using languages. However, determining potential neuroprotective effects of bilingualism in the elderly requires structural studies of older bilingual and monolingual individuals. Such studies exist but are currently few in number (for reviews, see Gold, 2015; Perani & Abutalebi, 2015). We consider two such studies in the following.

In pioneering research, Luk, Bialystok, Craik, and Grady (2011) compared white matter integrity in a sample of lifelong bilingual adults (with the L2 learned before the age of 11) and monolingual adults matched for age (mean age = 70 years) and performance on neuropsychological tests. Diffusion tensor imaging (DTI) (see Catani & Forkel, Chapter 9 in this volume) revealed greater white matter integrity in the corpus callosum and a number of major long-range tracts of the language network (the bilateral superior longitudinal fasciculi, right inferior fronto-occipital fasciculus, and uncinate fasciculus) (see also data from bilingual children, Mohades et al., 2012). Enhanced white matter integrity may be the outcome of the repetitive demands on the mechanisms of language control. Indeed, resting-state data in the same study showed significantly stronger distributed functional connectivity in bilinguals. Whereas monolinguals showed greater connectivity within frontal regions, bilinguals showed enhanced connectivity between regions associated with language control (left inferior frontal and left caudate) and posterior regions of tracts in the language network (see also Grady, Luk, Craik, & Bialystok, 2015). The results of Luk et al. (2011) usefully corroborate a structure (white matter) and functional correspondence (the resting-state data). They are tantalizing clinically because progressive disruption of white matter is typical of the aging brain (Gunning-Dixon, Brickman, Cheng & Alexopoulos, 2009; Pfefferbaum, Adalsteinson, & Sullivan, 2005) and disruption of prefrontal networks predicts impaired cognitive control (Mayda, Westphal, Carter, & DeCarli, 2011). Maintained integrity of white-matter tracts, as Luk et al. suggested, may compensate for gray matter atrophy. Gold, Johnson, and Powell (2013) found a different pattern in a sample of 60-year-olds and suggested that compensation in fact arose from increased cognitive control skills associated with bilingualism. Work showing increased gray matter in the ACC for older bilinguals compared to aged-matched controls may offer support for this position (Abutalebi et al., 2015b), but clearly there is a need for further work that includes a range of cognitive control and linguistic tasks.

Our second study investigated gray matter density differences between elderly bilingual and monolingual speakers. Bilinguals, compared to aged-matched monolinguals (with equivalent scores on education, socioeconomic status, and cognitive performance) displayed increased gray matter volume bilaterally in the temporal poles and the orbitofrontal cortex (Abutalebi et al., 2014). Interestingly, L2 proficiency also correlated with increased gray matter volume in the left anterior temporal pole, indicating that increased control demands may continue to shape the structure of the regions they target. Such an outcome is provocative because the temporal poles, along with the orbitofrontal cortex, are among the earliest cortical regions to suffer age-related brain atrophy (Kalpouzos et al., 2009).

Only further research can corroborate the indicative white matter and gray matter differences in the brains of elderly bilingual and monolinguals speakers that we have described. Where groups are matched on relevant explanatory variables (socioeconomic status, education, exercise), bilingual experience is plausibly causative (see García-Pentón, García, Costello, Duñabeita, & Carreiras, 2016, and commentaries for critical discussion). However, in line with the adaptive control hypothesis (Green & Abutalebi, 2013), the precise nature of the bilingual experience, accumulated and maintained over time, should be decisive in terms of the impact of bilingualism on the language-control network and its interaction with the language network. If so, it follows, as we briefly consider in the next section, that exploring such individual differences may prove critical in refining our understanding of the potential protective effects of bilingualism. Whether bilingual experience is directly, or indirectly, related to the integrity of the language-control network, and its interaction with the language network, requires identification and use of other markers of aging. It is conceivable, for example, that the mental challenge of language use in bilinguals is sufficient to maintain the integrity of a system in the brainstem: the locus coeruleus-norepinephrine system that helps prevent age-related neuronal damage (Mather & Harley, 2016). Bilingual experience would then be an indirect neuroprotective factor.

Conclusions and Future Prospects

We have endeavored to illustrate how the brain adapts to the experience of learning and using a further language. Fundamental to that experience is the way a speaker engages with the language practices of the communities in which they participate. From a theoretical point of view, the recurrent patterns of conversational exchange impose different demands on the processes of language control and induce different habits of language control (Green, 2011; Green & Abutalebi, 2013). For example, in some communities, speakers switch between their two languages to address different speakers. Despite potential activation, words and structures from the current, nontarget language must be blocked from the speech plan. In such circumstances, selection of one language involves non-selection of the other: language control is competitive. Other communities foster dense code-switching between languages and thus free the speaker to access resources from either language in order to achieve the communicative goal. Language control is cooperative: there is no target language, and output reflects momentary fitness in the speech plan (Green & Wei, 2014). These different contexts (the behavioral ecologies of language use) and the range of contexts that speakers inhabit mean that we need to describe in detail the nature of the contexts that shape adaptive response.

Current research indicates an unanticipated neuroplasticity of the bilingual brain. However, malleability is not unconstrained: there can be traces of early language experience. Intriguing data on international adoptees with early exposure to Chinese tone but with no later exposure showed that their neural response in a lexical tone discrimination task matched that of Chinese-French bilinguals exposed to Chinese from birth but differed from that of French speakers (Pierce, Klein, Chen, Delcenserie, & Genesee, 2014). Of equal importance is that such early experience influences the processing of the adopted language. In a French phonological working-memory task, international adoptees who were no longer exposed to Mandarin and who spoke only French differed from monolingual French speakers in the neural regions they recruited. Together with bilingual Mandarin-French speakers, they recruited regions typically associated with the control of language in order to perform the task to the same level (Pierce, Chen, Delcenserie, Genesee, & Klein, 2015). Early language experience may then shape the recruitment of regions involved in language control when processing the current native language. Such data point to the methodological need to use tasks that challenge the neural representation of language and its control in order to determine the nature of individual variety. Understanding such variety is essential to the construction of a theory of adaptive change in the bilingual brain. How exactly do control regions work together to perform a given task? This requires researchers to test causal models (i.e., to examine effective connectivity). Such models can also allow researchers to explore how engagement of control regions changes with language proficiency or as function of acquisition history.

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CHAPTER 12

LANGUAGE AND AGING

JONATHAN E. PEELLE

Introduction

As we age, sensory and cognitive changes occur that create challenges for language processing. At the same time, we gain increased experience and expertise with language and may adopt more efficient processing strategies. These complementary facets of normal aging suggest that age-related changes in language processing will be multifactorial.

Understanding language processing in older adulthood is important for both practical and theoretical reasons. Practically, a mechanistic understanding of how older brains process language may help an increasingly aging population communicate. From a theoretical standpoint, predictions made regarding how sensory and cognitive factors jointly contribute to language processing should be borne out in older adults, who typically show more variability than their younger counterparts in both of these domains. That is, normal aging is just one example of neuroanatomical and behavioral variability that can be useful to test theoretically important issues in neurolinguistics. For example, to what degree is language processing modular (Fodor, 1983)? If older adults show different patterns of neural processing during language processing from those observed in young adults, what implications might this have for our understanding of cognitive organization? Healthy aging is therefore a useful model for studying behavioral success in the presence of changing biology, and the lessons learned have implications for a variety of demographic and clinical populations.

In this chapter, I present an overview of some of the main themes associated with cognitive aging, followed by specific examples of how older adults process language, focusing on neural mechanisms wherever possible (for comprehensive reviews of behavioral findings, see Kemper, 1992; Wingfield & Stine-Morrow, 2000). Although I will focus on spoken language, many of the general principles also hold true for written and signed language.

COGNITIVE AGING

Language processing in older adults can only be understood within a broader picture of age-related cognitive change and mechanisms related to neural adjustment and compensation. I thus begin with a brief overview of the key points in the cognitive aging literature, many of which return more specifically in the context of language processing.

Age-Related Changes in Brain Structure and Cognitive Function

As we age, our brains get smaller and lighter: gyri widen and ventricles enlarge to a degree that is apparent to the naked eye on structural brain scans. It is not surprising then, to find significant reductions in gray matter volume and cortical thickness in older adulthood (Good et al., 2001; Raz et al., 1997; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Raz et al., 2005; Salat et al., 2004). Historically, age-related changes in gray matter have been discussed most often in the context of frontal and prefrontal cortex (Raz et al., 1997), although there are age-related changes in nearly every region of the brain (Fjell et al., 2009; Peelle, Cusack, & Henson, 2012). Changes in the composition of white matter are also common (Salat et al., 2005) and are typically measured using fractional anisotropy or other diffusion coefficients from diffusion-weighted imaging (see Catani & Forkel, Chapter 9 in this volume). White matter changes are frequently interpreted as relating to demyelination and thus less efficient communication between brain regions, although caution should be used when interpreting diffusion-weighted measures (Jones, Knösche, & Turner, 2013).

It is important to keep in mind methodological issues, such as changes in image contrast mechanisms associated with age (Salat et al., 2009) or the interpretation of regional change relative to global effects (Peelle et al., 2012), which may affect these results. Nevertheless, there is clear evidence that our brains change as we age, even in the absence of neurodegenerative disease.

In addition to widespread neuroanatomical change, healthy aging is also associated with altered cognitive processing across a wide number of domains, including working memory (Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000), attention and inhibitory control (Hasher, Stoltzfus, Zacks, & Rypma, 1991), general processing speed constructs (Salthouse, 1996), and many others. Verbal knowledge is typically well preserved (and frequently increases with age, as evidenced by increasing vocabulary sizes; Verhaeghen, 2003), but nearly every other domain studied by cognitive aging researchers reveals significant age-related changes in accuracy, reaction time, or processing strategy (Hedden & Gabrieli, 2004).

Adaptive Processing and Compensation in Older Adulthood

Given the concomitant neuroanatomical and cognitive changes that occur in normal aging, it would be surprising if older adults achieved a behavioral outcome with identical neural processes to those of young adults. As a first step, it can also be useful to examine differences in neural processing at the group level. Are there any consistent patterns that distinguish older adults' successful processing?

Since the early days of functional brain imaging, a frequent observation is that older adults tend to show less activity than young adults in the regions associated with that task in young adults, but increased activity in other regions (Grady, 2000). For example, Cabeza and colleagues (1997) performed a positron emission tomography (PET) study of memory for pairs of words, and noted that older adults appeared to show reduced activity during encoding compared to the young adults (and increased bilateral activity during retrieval, discussed in more detail later in this chapter). Reports of underactivation—that is, older adults showing reduced activity compared to young adults in what are assumed to be "core" processing areas for a task—have led to the suggestion that neural processing in older adults is less specialized than that of young adults (Park et al., 2004). The concurrent increases in activity viewed outside core regions are often viewed as compensatory, reflecting an older brain making up for lost processing efficiency by recruiting additional resources. Interpreting the older adults' "overactivation" as a beneficial adaptation has intuitive appeal, and is also supported by studies in which older adults' extra activity is correlated with behavioral accuracy. (However, such a correlation is not always found, meaning that compensation-related explanations for age-related differences in brain activity need to be viewed with caution.)

As hinted at earlier, a number of early studies examining age-related differences in neural processing used tasks in which young adults showed left-lateralized activation (that is, hemispheric asymmetry). When older adults performed the same task successfully, they frequently showed activity in the contralateral homologous region, and thus a lesser degree of hemispheric asymmetry. In Cabeza et al. (1997), for example, the authors found that during retrieval young adults showed right-lateralized activity in frontal cortex, whereas older adults showed bilateral activity in the same task. Although at the time it was uncommon to statistically assess the degree of lateralization in neuroimaging studies, qualitative results strongly suggested age differences in the degree of lateralized activity, at least for some tasks. Findings such as these led to the Hemispheric Asymmetry Reduction in OLDer adults (HAROLD) model (Cabeza, 2002), which proposed that reduction in hemispheric asymmetry is a key feature of neural processing in older adulthood, and is thus a guiding principle often used to consider age differences in activity. Additional frameworks proposing a key role for neural compensation in aging include the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz & Lustig, 2005) and the Scaffolding Theory of Aging and Cognition (STAC; Reuter-Lorenz & Park, 2014). CRUNCH and STAC also focus on the importance of compensatory activity, but are more agnostic about the specific type of activity to be expected (that is, there is less emphasis on reductions in lateralization). What these models have in common is that all propose that increased activity is needed for older adults to maintain the same performance as young adults.

An important question concerns the nature of the compensatory "resources" older adults up-regulate. What are these additional cognitive processes? One way to answer this question is to classify them as domain-preferential or domain-general. At a broad level, HAROLD-type activation may be considered as tending more toward the domain-preferential end of the spectrum, under the assumption that contralateral homologous regions frequently perform related functions. In contrast, another type of compensation would reflect up-regulation of domain-general systems such as executive attention networks (Duncan, 2010; Power & Petersen, 2013). These networks are considered domain-general because they can be dynamically engaged in the context of current task demands and goals, flexibly coding task-relevant information (Stokes et al., 2013; Woolgar, Hampshire, Thompson, & Duncan, 2011). Examples of both are seen during language processing.

Keeping in mind the brain's ability to flexibly compensate for task-related challenge, successful aging can be seen as relying on the relationship between supply and demand of processing resources (Figure 12.1). Processing efficiency reflects the degree to which any individual has a neurocognitive capacity relevant for a given task; demand is determined by the current task requirements, which for language tasks might consist of the joint challenges of perceptual, sensory, and meta-linguistic (i.e., thinking about the use of language) processing. If an individual's neural resources are sufficient to meet the demand, performance will be high. If not, performance will begin to deteriorate. Poor performance thus results from a mismatch between cognitive supply and demand. (In some sense, this can be thought of equally as reflecting too great of a behavioral challenge or

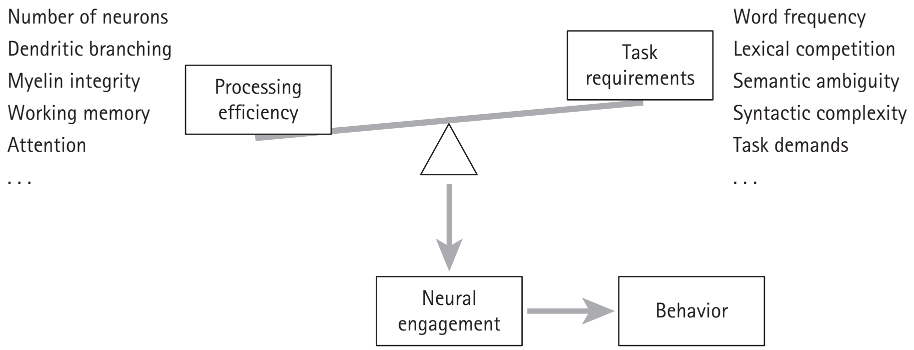

FIGURE 12.1. Schematic framework within which to consider the neural networks supporting language processing. The neural systems engaged and degree of behavioral success reflect a complex balance between the specific task requirements (including the level of linguistic processing required) and the level of cognitive resources listeners have available (which is tied to underlying neurophysiology).

too few neural resources, although the degree to which this distinction matters is an open question.)

Finally, as with structural magnetic resonance imaging (MRI) data, it is important to consider methodological concerns that might lead to age-related changes in functional measures that are unrelated to cognitive processing. These include differences in the shape or timing of the hemodynamic response (D'Esposito, Zarahn, Aguirre, & Rypma, 1999), neurovascular coupling (Tsvetanov et al., 2015), and movement within the scanner that may affect estimates of activity or network connectivity (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Increased variability in the timing of neural responses can also significantly impact group-averaged event-related potentials (ERPs).

Having thus briefly set the stage with a general framework for successful performance in normal aging, I now turn to reviewing comprehension and production of language in older adulthood as specific applications of these general principles.

Language Comprehension in Normal Aging

Most neuroantomically constrained models of spoken language comprehension have been formulated based on known anatomical connectivity, behavioral data from stroke patients, and functional brain imaging in healthy (typically young) adults. There is good general agreement on the importance of bilateral temporal cortex for auditory and single-word processing, extending into left lateral temporal cortex and inferior frontal gyrus (IFG) in the context of sentence-level material (Hickok & Poeppel, 2007; see, in this volume, Poeppel, Cogan, Davidesco, & Flinker, Chapter 26, and Bornkessel-Schlesewsky & Schlesewsky, Chapter 27; Peelle, Johnsrude, & Davis, 2010; Rauschecker & Scott, 2009). However, much less is known regarding how these networks change in the context of healthy aging. In the following subsections, I discuss patterns of neural processing for language in older adults relative to those seen in young adults, some illustrations of which are shown in Figure 12.2.

Word Perception

Contemporary theories of spoken word perception frequently operate within a lexical competition framework in which listeners must correctly identify a target word by inhibiting (or not selecting) similar-sounding items in the lexicon (Gagnepain, Henson, & Davis, 2012; Luce & Pisoni, 1998; Marslen-Wilson & Tyler, 1980; Norris & McQueen, 2008). Behaviorally, older adults have more difficulty recognizing spoken words, particularly in noise (Dubno, Dirks, & Morgan, 1984; Pichora-Fuller, Schneider, & Daneman, 1995), and studies show that older adults' spoken-word processing is affected by both lexical and

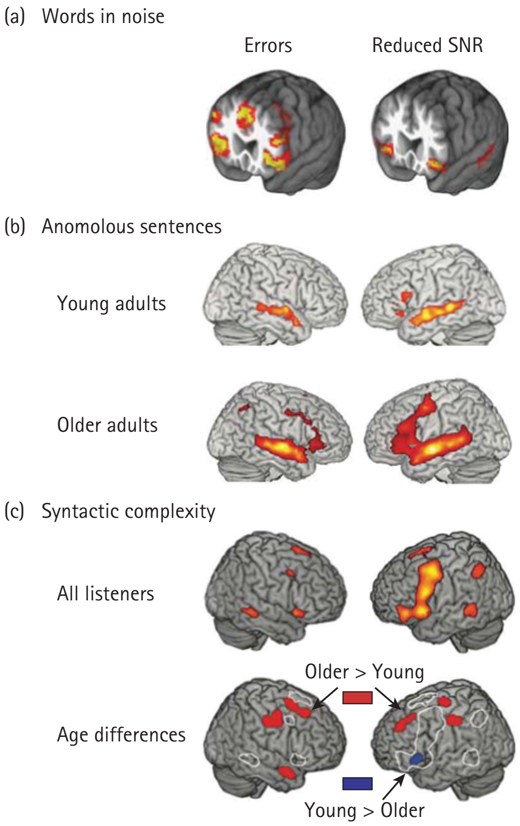

FIGURE 12.2. (A) Increased activity in the cingulo-opercular network during spoken word processing in response to both errors and poorer signal-to-noise ratio (SNR).

Source: Vaden, et al., *Journal of Neuroscience* (2015). Permission granted.

(B) Activity for spoken sentences with anomalous prose in young and older adults during a target word-monitoring task (Tyler, et al., 2010). Older adults show increased activity in right frontal cortex to support sentence comprehension.

(C) Regions showing differential activation for spoken sentences with subject-relative versus subject-relative embedded clauses (Peelle, Troiani, et al., 2010). Older adults show less activity in left inferior frontal gyrus, but greater activity in regions of prefrontal cortex outside the common syntax network.

Source: Used with permission of Oxford University Press; License number 3756501173119.

cognitive factors (Humes, Kidd, & Lentz, 2013; Lash, Rogers, Zoller, & Wingfield, 2013; Sommers & Danielson, 1999). What are the neural processes that are engaged?

Shafto and colleagues (2012) presented young and older adults with spoken words and nonwords that varied in both cohort competition (Marslen-Wilson, 1987) and imageability, along with a complex acoustic baseline. Young adults show increased activity in IFG as a function of increased lexical competition and selection demands (Zhuang, Tyler, Randall, Stamatakis, & Marslen-Wilson, 2014). In contrast, older adults appear to be less sensitive to competition and selection manipulations, although potentially more sensitive to imageability effects (Shafto et al., 2012). Research with visual word identification also suggests some age differences in processing that may dissociate lexical and sublexical components (Whiting et al., 2003). These studies suggest that even at the single-word level, well-known lexical properties may be processed differently in older adults compared to young adults.

Functional MRI (fMRI) studies of spoken word perception in older adults also implicate executive attention systems in speech perception when noise is present. Eckert and colleagues (2008) presented listeners with single spoken words that were low-pass filtered (to mimic the effects of high-frequency hearing loss); intelligibility varied as a function of the cutoff frequency. Overall intelligibility across age groups was equated using broadband noise. On each trial, listeners repeated the presented word back if possible, providing a trial-by-trial measure of recognition accuracy. For correct trials, older adults showed different patterns of activation compared to young adults, with increased activity in middle frontal gyrus, anterior cingulate, and visual cortex. These results suggest that in challenging listening situations, older adults rely to a greater degree on executive attention mechanisms (middle frontal gyrus and anterior cingulate) than do young adults, even when they are successful.

It is difficult to talk about the neural systems contributing to speech perception in adverse listening conditions without discussing the cingulo-opercular network. The cingulo-opercular network is part of the multiple-demand network, comprising the dorsal anterior cingulate and bilateral frontal operculum (or anterior insula, depending on the characterization) (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Duncan, 2010; Power & Petersen, 2013). Across a variety of tasks, the cingulo-opercular network shows elevated responses for sustained attention and error trials (Neta et al., 2015). In spoken-word processing, elevated cingulo-opercular activity is seen in speech comprehension tasks when the acoustic signal is degraded enough to result in reduced intelligibility (and thus behavioral errors), including in older adults (Eckert et al., 2009). Further evidence for the functional role of the cingulo-opercular network in language processing comes from studies examining whether activity following one trial can predict accuracy on the next. Vaden and colleagues (2015) examined this issue using general linear mixed-model analysis to predict the accuracy of participants' single-word recognition in multi-talker babble. The authors found, first, that activity in older adults' cingulo-opercular network predicted their accuracy on a subsequent trial, and, second, that the level of cingulo-opercular modulation was lower for older adults than for young adults (Vaden et al., 2013). These findings implicate cognitive control mechanisms supported by the cingulo-opercular network in single-word perception.

Of course, regions beyond the cingulo-opercular network have also been implicated in older adults' word perception. Kuchinsky and colleagues (2012) also presented single words that had been bandpass filtered to different levels in order to manipulate intelligibility. As expected, word perception was associated with bilateral temporal cortex activity. Both increasing age and decreasing word intelligibility were associated with more activation in occipital cortex. Interestingly, occipital cortex was functionally connected to left temporal cortex (including middle temporal cortex, superior temporal gyrus, and

Heschl's gyrus), suggesting that it may have a relationship to task-relevant processing. These results suggest that cross-modal attention to speech cues may be impacted by age, as well as by the quality of the auditory stimuli being presented.

In summary, single-word processing in older adults appears to be supported broadly by similar systems to those used by young adults—namely, bilateral temporal cortex. However, differences have been reported with respect to psycholinguistic and attentional factors. Published studies to date suggest that older adults use a more extensive set of brain regions when processing single words, and suggest a complex interaction between brain structure, brain function, and behavior (Bilodeau-Mercure, Lortie, Sato, Guitton, & Tremblay, 2015). A further point is that the acoustic clarity of items (including age-related changes in hearing sensitivity) appears to have a significant impact; I return to the important issue of perceptual challenge in more detail in the following.

Sentence Comprehension

In addition to the phonological, lexical, and semantic computations involved in single-word perception, sentences require additional processes related to correctly parsing the syntax of an utterance, and frequently contain words (such as pronouns or ambiguous words) that require context to interpret (Rodd, Johnsrude, & Davis, 2012). These added complexities mean that spoken sentences generally rely on a broader network of brain regions than that required for single words, including more extensive regions of bilateral temporal cortex and left IFG (Peelle, 2012).

A productive line of research on semantic processing has used electroencephalography (EEG) (see Leckey & Federmeier, Chapter 3 in this volume) to investigate time-locked activity to words occurring with different levels of preceding predictability. These studies therefore assess the ability of listeners to make use of semantic context during online sentence comprehension. Federmeier and Kutas (2005) presented young and older adults with written sentences in which the final word was highly predictable (e.g., "No one at the reunion recognized Dan because he had grown a beard") or not very predictable (e.g., "At the children's park next to the beach she saw a man with a beard"). Young adults showed a pronounced difference in time-locked response between strongly and weakly constrained sentences, an expected N400 response (Kutas & Hillyard, 1984). In contrast, older adults as a group showed less difference between the strongly and weakly constrained sentence types, suggesting that older adults may be less able to use contextual constraints during online sentence processing (Wlotko, Federmeier, & Kutas, 2012). Later studies suggest that individual differences exist, with some older adults showing patterns that are more similar to those seen in young adults (Federmeier, Kutas, & Schul, 2010). (These online EEG measures can be contrasted with behavioral measures that frequently show older adults showing greater reliance on context compared to young adults [Dubno, Ahlstrom, & Horwitz, 2000; Pichora-Fuller, et al., 1995; Wingfield, Aberdeen, & Stine, 1991].)

Behaviorally, there is considerable evidence that older adults have difficulty processing syntactically complex sentences, including reduced use of grammatical complexity in production (Kemper, Greiner, Marquis, Prenovost, & Mitzner, 2001; Kemper, Marquis, & Thompson, 2001), and differentially longer response times on comprehension tasks (Kemtes & Kemper, 1997; Waters & Caplan, 2001; Wingfield, Peelle, & Grossman, 2003). Functional neuroimaging studies of age-related changes in sentence processing have reported at least two patterns of results.

In the first fMRI study, young and older adults were presented with short spoken sentences that contained either a subject-relative or object-relative center-embedded clause, making a keypress response to indicate the gender of the character performing the action (Peelle, Troiani, Wingfield, & Grossman, 2010). For example, when hearing the sentence "Brothers that sisters assist are happy," participants would press a button to indicate that a female is performing the action (in this case, assisting). Older adults' accuracy was generally high on this task, consistent with a high level of successful comprehension. Both young and older listeners showed increased activity for the more complex object-relative sentences compared to subject-relative sentences. However, older adults showed less activity than the young adults in left ventral IFG, and increased activity in regions of dorsolateral prefrontal cortex and premotor cortex. Thus, to maintain high levels of sentence comprehension accuracy, older adults showed additional frontal recruitment.

Tyler and colleagues (2010) took a slightly different approach, having young and older participants perform a word-monitoring task in sentences with normal prose, anomalous prose, and random word lists. The anomalous prose sentences were grammatically correct but did not convey a coherent meaning (e.g., "Stephen didn't catch himself very much. Her tooth was driven because he had a weak nail and she couldn't heat anyone properly."). The authors focused on regions showing increased activation for the anomalous prose condition compared to an acoustic baseline. Overall, as in Peelle et al. (2010), young and older adults relied on a largely similar network of regions (bilateral superior temporal gyrus and left IFG), although there was some indication that older adults showed increased activity in the right IFG. Most interesting, however, was a second analysis in which they looked at whether individual differences in gray matter in left IFG were related to the activation they saw in right IFG. Indeed, older listeners with reduced gray matter in left IFG and left middle temporal gyrus showed increased activity in right hemisphere homologues of these regions, producing a more bilateral pattern of activation in the older adults relative to young adults. Importantly, these findings suggest that individual differences in cortical integrity may help explain patterns of compensatory activity.

A critical distinction to consider is whether processing is interpretive (occurring when the meaning of the sentence is being calculated) or post-interpretive (occurring after the meaning has been determined). A classic example of post-interpretive processing would be making a meta-linguistic decision about a sentence, such as whether it is grammatically appropriate. These two stages may also be thought of as "online" (interpretive) versus "offline" (post-interpretive) processing. The online–offline distinction may be particularly important in the context of experimental paradigms requiring a response (such as a button press, or recall) from participants, as this adds task-related cognitive demands that are likely separate from those required for comprehension (Davis, Zhuang, Wright, & Tyler, 2014). It has been argued that older adults show similar online processing to that of young adults, but differences in offline processing (Caplan & Waters, 1999; Waters & Caplan, 2001). Alternatively, others have suggested that domain-general cognitive systems are required for interpreting challenging sentences, and not simply for meta-linguistic decisions (Wingfield & Grossman, 2006). Although it seems likely that both levels of processing are affected during aging, the issue remains a topic of debate.

In summary, age differences in neural activity during sentence comprehension are routinely observed, particularly when semantic or syntactic challenges are explicitly introduced. However, disagreement persists regarding the degree to which these reflect online versus offline processing demands, and whether they reflect domain-preferential or domain-general cognitive processes.

Perceptual Challenge and Effortful Listening

Normal aging is associated with changes at nearly every level of the auditory system (Peelle & Wingfield, 2016). Loss of hearing sensitivity is common in normal aging, particularly in higher frequencies (Morrell, Gordon-Salant, Pearson, Brant, & Fozard, 1996). Other age-related changes in hearing include broadening frequency filters and reduced accuracy of temporal processing (Humes, Kewley-Port, Fogerty, & Kinney, 2010; Schneider, 1997). Thus, understanding the processes supporting speech comprehension in older adults requires considering the effects of reduced auditory sensitivity.

Subjectively, hearing impairment is frequently associated with “effortful” listening (Pichora-Fuller et al., 2016). There is growing evidence that listening effort reflects, in part, additional cognitive processing that is required to make sense of degraded speech (Rönnberg et al., 2013; Wingfield, Tun, & McCoy, 2005). The role of acoustic challenge on word perception is seen in cases where adding external noise decreases intelligibility in proportion to how many phonological neighbors a word has—that is, the more lexical competitors, the more difficult accurate perception becomes (Luce & Pisoni, 1998), particularly for older adults (Sommers, 1996). Hearing loss similarly affects perception, with hearing-impaired listeners requiring more acoustic information before identifying a word (Lash et al., 2013).

Some of the most compelling behavioral evidence for the cognitive consequences of acoustic challenge comes from episodic memory paradigms in which listeners are asked to recall lists of unrelated words or digits, some of which are presented in noise. In these situations, memory is worse not only for the item presented in noise, but also for *previous* items that were not degraded (Piquado, Cousins, Wingfield, & Miller, 2010; Rabbitt, 1968). The disruption of memory encoding is consistent with increased working-memory resources being needed to comprehend noisy speech (Cousins, Dar, Wingfield, & Miller, 2014; Miller & Wingfield, 2010). Memory effects for spoken language are also seen in participants with age-related hearing loss (McCoy et al., 2005;

Rabbitt, 1991), although depending on the specific task, individual differences in hearing ability may not correlate with memory measures (Ward, Rogers, Van Engen, & Peelle, 2016).

Neuroimaging evidence for effects of perceptual challenge in older adults has been discussed earlier for words that have been acoustically degraded through background noise or low-pass filtering (Eckert et al., 2009; Eckert et al., 2008; Vaden et al., 2015). Additional support is emerging in the context of spoken sentences. Erb and Obleser (2013) presented spoken sentences to young and older adults; the sentences were normal or acoustically degraded using noise vocoding with four channels. Noise vocoding reduces the spectral detail in the speech, but leaves the temporal amplitude envelope preserved (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995); speech vocoded with four channels is typically somewhat intelligible. The authors found that older adults showed increased activation in dorsal anterior cingulate cortex in response to degraded speech compared to the younger adults. Furthermore, individual differences in activity in this region were positively correlated with word-report scores, suggesting a functional role for this increased activity.

In summary, there is ample behavioral evidence that perceptual challenges caused by acoustic degradation or distortion can alter the neural processes required for spoken language comprehension. Although particularly relevant in the context of age-related hearing loss, these same principles also likely apply in the case of background noise (Scott & McGettigan, 2013), competing talkers, or non-native accents (Van Engen & Peelle, 2014). Thus, again, issues raised in the context of normal aging have broad implications for models of speech perception.

Language Production in Normal Aging

Syllable Production

Older adults experience more word-finding failures and more filled pauses (for example, saying "um") during speech production, along with overall slower rates of production (Duchin & Mysak, 1987). These production challenges might be caused by difficulty with lexical retrieval, difficulty accessing the correct speech sounds (phonology) associated with a lexical item, or difficulty forming the appropriate motor plan. The fact that older adults take longer to make sequential speech movements and make more articulatory errors (Bilodeau-Mercure et al., 2015) is consistent with at least some age effect on motor planning or production.

Sörös and colleagues (2011) had young and older adults produce syllabic sounds (the vowel /a/ and the multisyllabic token /pa-ta-ka) in an fMRI study. They found significantly lower activity in older adults in bilateral temporal cortex (near primary and secondary auditory cortex), but significantly more activity in older adults in bilateral middle temporal gyrus and large portions of bilateral frontal cortex. Tremblay and

Deschamps (2016) investigated the relationship of brain structure for young and older adults producing sequences of syllables that were simple (e.g., /pa-pa-pa-pa-pa-pa/) or complex (e.g., /pa-ta-ka-pa-ta-ka/). Behaviorally, older adults took longer, and were less accurate, in their production compared to young adults. Individual differences in speech production behavior correlated with regions of temporal and frontal cortex that also showed age-related decreases in cortical thickness in the same participants. Together these findings suggest a link between age-related neuroanatomical change and concomitant alterations in speech production.

Word Retrieval and Picture Naming

There is ample evidence that age-related differences in speech production go beyond motor planning. Speech production is frequently assessed in the context of object naming, which beyond visual object recognition requires retrieving the name of an object (lexical information) and its corresponding phonological form prior to producing it (Indefrey & Levelt, 2004). During picture-naming tasks, older adults often have more difficulty producing correct names for pictures than young adults, particularly for low-frequency items (Nicholas, Obler, Albert, & Goodglass, 1985; Rogalski, Peelle, & Reilly, 2011). Weirenga and colleagues (2008) used fMRI to examine neural activity during picture naming in young and older adults. Although there were no age differences in accuracy, older adults appeared to show increased activity in several regions of both temporal and frontal cortex, including right IFG and bilateral insula. Individual differences in activity in several of these regions showed positive correlations with accuracy.

Perhaps the most compelling evidence for age-related difficulties in word retrieval is found in the tip-of-the-tongue (TOT) experience, in which a speaker is certain they know a word but is unable to produce it (for example, in response to the question, “what is the name of the strait between Alaska and Siberia?”). Older adults experience TOT states significantly more often than young adults, particularly for proper nouns (Burke, MacKay, Worthley, & Wade, 1991). Phonological (homophone) priming improves older adults’ retrieval of proper names (Burke, Locantore, Austin, & Chase, 2004), suggesting that difficulty retrieving phonological information may underlie these TOT states; that is, semantic and/or lexical information has been accessed (resulting in a strong feeling of knowing), but phonological retrieval has not yet occurred (preventing the word from being produced).

In an effort to identify the neural systems involved in TOT states, Shafto and colleagues (2007) examined gray matter density and TOT occurrence in older adults, and found that increased TOTs were associated with reduced gray matter in the left insula and anterior cingulate cortex. These findings were anatomically dissociable from regions of gray matter that correlated with scores on an executive processing task (Ravens progressive matrices), suggesting that age-related changes in TOTs are not simply reflecting an overall cognitive decline. Converging evidence from fMRI on a similar experiment also showed increased left anterior insula activity for TOT states

(Shafto, Stamatakis, Tam, & Tyler, 2010). (It is interesting to consider these structural findings in the anterior insula in the context of the error-related activity often reported in the cingulo-opercular network—it may be that TOTs are related to general states of attention and error-monitoring seen in the cases of perceptual errors.)

Aging is thus associated with differences in picture naming and word production. Although some of these differences may be due to changes in articulatory fluency or control, there is also evidence suggesting age-related changes to lexical or phonological retrieval stages of processing.

Sentence and Discourse Production

In comparison to single-word production and naming, there has been little work on the cognitive neuroscience of sentence or discourse production in healthy aging. However, it is worth briefly noting that a number of striking behavioral age differences have been observed. A particularly interesting way of assessing sentence production is to examine diaries or other writing samples produced over time. In these cases, the complexity of written sentences has been found to decrease over time (Kemper, 1987; Kemper, Greiner, et al., 2001). This includes decreases in syntactic complexity and idea density. Provocatively, longitudinal studies have found that the linguistic complexity of writing samples in early life has been found to predict development of Alzheimer's disease in older age (Snowdon et al., 1996). Measures of speech production in the context of storytelling can also help distinguish between patients with a variety of neurodegenerative diseases (Ash et al., 2006; Ash et al., 2014). Thus, connected speech offers a number of additional insights into language production that may not be available with word or picture naming.

Aging and the Effects of Multilingualism on Language Processing and Cognitive Function

Recent years have seen increasing interest in the effects of bilingualism (or more generally, multilingualism) on language and cognitive processing (see, in this volume, Green & Kroll, Chapter 11, and Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24). Multilingualism presents a number of complex cognitive challenges. For example, storing multiple lexicons may provide extra linguistic support, but also requires choosing between a greater number of words referring to an intended concept. Code switching—that is, changing from one language to another in production (or comprehension)—also requires cognitive control and flexibility (Gollan & Ferreira, 2009; Olson, 2017). Because of these added demands, multilingualism is frequently associated with inhibition and task-switching (Abutalebi & Green, 2008; De Baene, Duyck, Brass, & Carreiras, 2015; Green & Abutalebi, 2013). Multilingualism is also associated with a number of neural changes, including functional processing changes in the caudate (Crinion et al., 2006), and structural changes in left frontal and parietal cortices (Grogan et al., 2012; Mechelli et al., 2004; Stein et al., 2012). Although some potential converging links may be observed between specific brain regions and cognitive processes implicated in multilingual processing, the correspondence is not always straightforward (Higby, Kim, & Obler, 2013).

Given age-related changes in cognitive function, it interesting to consider how multilingualism fits into the aging process. In particular, an area of burgeoning interest is the degree to which bilingualism may lead to improved cognitive processing, especially in older age (Bak, Nissan, Allerhand, & Deary, 2014; Bialystok, Craik, & Luk, 2012; Kavé, Eyal, Shorek, & Cohen-Mansfield, 2008). Early behavioral work suggested that bilingualism was associated with altered executive processing (Bialystok, Craik, Klein, & Viswanathan, 2004; Prior & MacWhinney, 2009), a finding that also has found some support in brain imaging studies (Gold, Johnson, & Powell, 2013; Gold, Kim, Johnson, Kryscio, & Smith, 2013; Schweizer, Ware, Fischer, Craik, & Bialystok, 2012). One compelling hypothesis is that years of multilingual processing result in cognitive changes, building cognitive reserve that can have a protective effect against age-related cognitive decline (Craik, Bialystok, & Freedman, 2010). That being said, disagreement exists as to the extent to which bilingualism affects cognitive processing in older adults (Antón, García, Carreiras, & Duñabeitia, 2016), and further data are likely needed to fully resolve the issue.

BEYOND INDIVIDUAL BRAIN REGIONS: NETWORK BALANCE DURING LANGUAGE PROCESSING

Owing in part to the prominent role that language processing has played in the history of localizing brain function, it can be tempting to think about age-related changes in neural activity in terms of discrete regions being activated differently in older adults compared to young adults. Although there is some truth to be found from this perspective, a more accurate framework is likely one in which individual differences in sensory and cognitive ability lead to altered dynamics of interacting brain networks (Shafto & Tyler, 2014). From this network-centered perspective, levels of activity in any given network arise naturally out of the balance between processing efficiency and task requirements illustrated in Figure 12.1. Individual differences in neurobiology, and concomitant sensory and cognitive ability, thus assume the primary explanatory position, rather than age per se. Operationally, a network-based perspective might be supported by analyses incorporating structural brain measures, functional brain measures, and behavior to investigate systematic variability across participants (Meunier, Stamatakis, & Tyler, 2014). Recent studies that have taken network-based approaches to aging suggest age-related changes in network connectivity (Tsvetanov et al., 2016) that underlie older adults success with at least some language tasks (Campbell et al., 2016).

Conclusions

Adult aging is an ideal framework within which to study how individual differences in cognitive and perceptual factors influence language processing. Evidence from functional brain imaging suggests that age-related changes in the neural underpinnings of language processing are present at nearly every level of linguistic processing—syllables, words, sentences, and discourse—in both production and comprehension. Thus, although language processing is generally well preserved in older adulthood, this behavioral success is accomplished using a different balance of cognitive and neural processing in older adults. Emerging work specifically looking at individual differences in older adults' brain activity is an exciting new direction. It may well be that improved measures of neural integrity, sensory acuity, and cognitive ability ultimately prove more useful in predicting language processing than chronological age.

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CHAPTER 13

LANGUAGE PLASTICITY IN EPILEPSY

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INTRODUCTION

EPILEPSY provides a rich context in which to study brain organization of language, and the plasticity of language organization in response to electrophysiological and structural disturbances. Clinically, issues regarding the localization of language areas often become central when pharmacologically refractory patients are considered for resective surgical treatment, as surgery can be an option for patients whose seizures arise from a focal brain region. Surgical resection for seizure control involves removal of the epileptogenic cortex that generates seizure activity, and thus, one of the main challenges of resective surgery is to remove a sufficient extent of epileptogenic brain tissue, yet without significant compromise to function. Depending on the location of the epileptogenic cortex and the proposed surgery, language is frequently at risk, and therefore various pre-surgical procedures are performed to assess and reduce this risk of postoperative language decline, mainly by identifying the location of essential language areas. It is these procedures that provide a unique and valuable opportunity to study language plasticity in epilepsy.

In the context of epilepsy surgery and risk to language function, there are two types of brain plasticity mechanisms to consider. The type most often associated with epilepsy is the reorganization of language that is attributed to the ongoing functional disruption or slowly progressive structural disturbances from chronic epileptic activity (Janszky, Mertens, Janszky, Ebner, & Woermann, 2006). This abnormal electrophysiological activity could shift language from the left to the right hemisphere or might reroute language pathways during development from traditional to nontraditional sites intra-hemispherically within the dominant left hemisphere (Duchowny et al., 1996; Liegeois et al., 2004). As the incidence of atypical language organization is significantly higher among people with epilepsy relative to the healthy population, the surgical team cannot simply rely on typical language landmarks (Berl et al., 2014; Helmstaedter, Kurthen, Linke, & Elger, 1997; Janszky, Jokeit, et al., 2003; Risse, Gates, & Fangman, 1997). Rather, disruptive techniques that capitalize on the "lesion method," such as Wada testing and electrocortical stimulation mapping, are frequently employed to determine hemispheric laterality and intra-hemispheric localization essential language areas. Activation techniques such as functional magnetic resonance imaging (fMRI) are increasingly utilized as well, although disruptive methods remain the gold standard (Hamberger, 2007).

In contrast to the slowly progressive changes related to chronic epileptiform activity, advances in noninvasive neuroimaging have brought to light the more acute changes in language organization that result from surgical resection. These changes may or may not coincide with recovery of function, and determining which factors are more or less likely to be associated with reorganization and recovery is currently fertile ground for research. Although acute brain injury is, unfortunately, not uncommon, such phenomena are typically unexpected, and premorbid conditions can only be inferred. Conversely, epilepsy surgery is planned in advance, and therefore offers the opportunity for thorough examination prior to resection, enabling within-subject, pre- and postoperative comparisons.

Clinically, both of these mechanisms play a role in surgical decision-making. The location of essential language areas must be identified in the individual patient, with the goal of sparing these regions from resection. However, in cases in which language areas might be disrupted, it would be helpful to predict which patients or which brain regions are more likely to undergo successful reorganization and recovery.

In the following sections, we present findings that have emerged from studies of both chronic epilepsy patients who may or may not have undergone progressive language reorganization during development, and patients assessed pre- and postoperatively who may have undergone acute language reorganization due to surgical intervention. These data are based primarily on findings from clinical tools, which include Wada testing, cortical stimulation, and neuroimaging, as well as language assessment. Drawing from both of these domains and these various methods, we consider the influence of demographic, clinical, and epilepsy-related factors that appear to influence progressive and acute brain plasticity of language.

Effects of Chronic Epilepsy

In considering language plasticity in epilepsy, it is important to note that epilepsy is a heterogeneous disorder, with individual variability in multiple factors that could potentially affect the cerebral organization of language. These include laterality and intra-hemispheric location of seizure onset and spread, underlying neuropathology, age of seizure onset, duration of epilepsy, handedness, seizure frequency, frequency and location of abnormal electroencephalogram (EEG) activity between seizures, and type, amount, and duration of pharmacological treatment. Most of the work on language organization in epilepsy has involved temporal lobe epilepsy (TLE) patients, mainly because these patients represent the largest and most homogenous subgroup of patients who undergo surgical treatment. Nevertheless, these patients vary with respect to many of the factors listed previously, as well as other factors that can influence language organization, including medial temporal versus lateral neocortical onset and presence/absence of hippocampal sclerosis (HS).

In many patients with focal epilepsy, structural abnormalities such as neoplasms of vascular malformations can be identified, and the ability to detect some of the more subtle morphological irregularities (e.g., sclerosis, dysplasia) has increasingly improved with advances in neuroimaging. On the other hand, some patients have no structural lesion identified, yet the brain tissue is functionally abnormal due to epileptiform activity (i.e., seizures and abnormal interictal electrophysiological discharges). Thus, chronic epilepsy can give rise to language reorganization in response to structural aberration, electrophysiological aberration, or the combination of these. Our knowledge regarding language plasticity in epilepsy comes primarily from Wada testing, which has brought to light variations in the hemispheric distribution of language, and electro-cortical mapping, which has revealed intra-hemispheric variations in the topography of brain areas that mediate language.

Alterations in Language Laterality: Evidence from Wada Testing

Wada testing is an invasive procedure that enables assessment of cognitive functioning during temporary anesthesia of one cerebral hemisphere, induced by injection of a short-acting anesthetic agent into the internal carotid artery (Wada & Rasmussen, 1960). The procedure was originally developed to determine hemispheric language dominance in epilepsy surgery candidates, and was subsequently modified to include assessment of hemispheric memory capacity as well (Milner, Branch, & Rasmussen, 1962). Given the territory perfused by the internal carotid artery, the procedure enables assessment of language ability in each cerebral hemisphere, separately, serving as a crude reversible model for the effects of surgical resection. Although the particular format of Wada testing varies among surgery centers, the hemispheric anesthetic effect is typically confirmed via scalp EEG (ipsilateral, unilateral slowing) and contralateral hemiplegia/hemiparesis. Language testing typically includes automatic speech (e.g., counting), object naming, repetition, execution of verbal commands, and reading. Unilateral language dominance is inferred when all tasks are performed accurately with anesthesia in one hemisphere, and inability to perform tasks with anesthesia of the contralateral cerebral hemisphere. Bilateral language representation is typically inferred when a combination of accurate and inaccurate performances occur following both left- and right-hemisphere anesthesia. Clinically, some centers determine hemispheric language representation based on qualitative observations, such as occurrence of speech arrest or presence of paraphasic errors, whereas others utilize more empirically based scoring methods with calculated laterality indices (Hamberger & Walczak, 1996; Loring, Meader, Lee, & King, 1992).

Prior to the advent of Wada testing, it was generally assumed that handedness could be used as an indicator of hemispheric language dominance. Wada testing with epilepsy patients revealed discrepancies in the relation between these two variables (Gloning, Gloning, Harb, & Quantember, 1969; Rasmussen & Milner, 1977; Rausch & Walsh, 1984). Wada testing in mixed neurological samples has shown right-hemisphere language dominance in approximately 4%–37% of right-handers and 25%–52% of left-handed or ambidextrous individuals (Branch, Milner, & Rasmussen, 1964; Helmstaedter et al., 1997; Loring et al., 1990; Mateer & Dodrill, 1983; Powell, Polkey, & Canavan, 1987; Rausch & Walsh, 1984; Rey, Dellatolas, Bancaud, & Talairach, 1988; Risse et al., 1997; Strauss & Wada, 1983; Woods, Dodrill, & Ojemann, 1988; Zatorre, 1989), whereas right-hemisphere language dominance in healthy individuals is estimated at approximately 4% based on Doppler sonography (Knecht et al., 2000).

Similar to that shown in lesion studies of patients with early left-hemisphere injury and increased likelihood of right-hemisphere language, left-hemisphere seizure onset has been shown to be the most significant predictor of atypical (i.e., right or bilateral) language representation (Branch et al., 1964; Loring et al., 1992). Rausch and Walsh (1984) found that 15% of their sample of right-handed patients with left TLE were right-hemisphere language dominant, and several investigators have reported a significant relation between of age of "injury" (e.g., left-cerebral injury, left-sided seizure onset) and atypical language lateralization (Rasmussen & Milner, 1977; Rausch, Boone, & Ary, 1991; Rey et al., 1988; Satz, Strauss, Wada, & Orsini, 1988; Strauss & Wada, 1983), with earlier age of injury, typically before age 5, more likely resulting in right or mixed language dominance. A retrospective study of 445 epilepsy patients who had undergone bilateral Wada testing found that 46% of left-handers with early left-hemisphere lesions were right-hemisphere language dominant, whereas 37% of left-handers with late neocortical left-hemisphere lesions were more likely to have bilateral language representation (Möddel, Lneweaver, Schuele, Reinholz, & Loddenkemper, 2009). These results suggest an influence of age of onset/injury, in that right dominance might reflect early insult, before left-hemisphere dominance is established, whereas bilateral language might reflect compromise to the left language system at a time when left-hemisphere dominance has already started to take hold.

These studies, however, fail to tease apart the effects of space-occupying lesions from more epilepsy-specific features. With this in mind, Janszky et al. (2003) used Wada testing to determine language dominance in a relatively homogenous subgroup of 184 TLE patients, all of whom had medial TLE (i.e., hippocampal seizure onset), and unilateral hippocampal sclerosis (HS), yet no other lesions, thereby eliminating the influence of type of pathology, location of pathology, and age of precipitating injury. HS is understood to occur during infancy or early childhood (Engel, Williamson, & Wieser, 1997), and is not adjacent to classic language areas. These investigators found that 24% of left medial temporal lobe epilepsy (MTLE) patients with HS had atypical hemispheric language. Moreover, atypical language representation in these patients was associated with a significantly higher frequency of interictal discharges and with sensory auras, which reflects seizure propagation to lateral temporal structures. These findings suggest that in addition to structural factors, functional factors such as abnormal EEG activity (i.e., interictal EEG discharges and seizure spread) can alter cerebral language organization.

Although Wada testing is a powerful disruptive technique, enabling assessment of language in a functionally isolated hemisphere, the procedure is limited in its rendering of a fairly diffuse unilateral lesion and its inability to provide information regarding intra-hemispheric organization of language. Electrical stimulation mapping, discussed in the following section, enables detailed intra-hemispheric testing of relatively small cortical areas, and thus could be considered a refined application of the lesion method.

Intra-hemispheric Variations: Evidence from Electrical Stimulation Mapping

Electrical stimulation mapping (ESM) is an invasive procedure in which electrical stimulation is applied briefly (~2–10 sec) to the cortical surface, producing a reversible functional lesion in the discrete region below the stimulating electrodes (Hamberger, 2011). The procedure is used to identify essential sensory, motor, or language areas when there is concern that the proposed brain surgery will involve removal or disruption of functional brain tissue. Sites identified as positive are typically spared from resection, with the goal of preserving function postoperatively. Although primarily used for clinical purposes, the procedure provides a unique opportunity to study the intra-hemispheric representation of language (Ojemann, 1983b; Penfield & Roberts, 1959). Nevertheless, in considering results from ESM studies, as with any technique, it is important to understand the nature of data that can be obtained, and the potential limitations of the procedure.

As noted earlier, ESM for the identification of language cortex utilizes the lesion method, and therefore relies on "negative" responses. That is, unlike ESM for the identification of sensory or motor cortex, which is based on stimulation-evoked "positive" responses such as subjective sensation (e.g., tingling) or observable movement (e.g., muscle twitch), stimulation of language cortex does not elicit language behavior. Instead, the patient must be engaged in a language task, and stimulation of language cortex will disrupt task performance. Theoretically, an ESM trial simulates the functional consequences of damage to the cortical site(s) being stimulated.

Several investigations have demonstrated topographical specificity of language functions using ESM; specifically, electro-cortical stimulation of a particular brain area can disrupt one language function (e.g., naming), yet a different function (e.g., reading) will remain intact during stimulation. Consequently, unless the particular function supported by the cortical area is tested during stimulation, the site could erroneously be classified as negative for language. Although this might suggest that a wide breadth of language functions should be tested at each site under consideration, practical considerations, such as time limitations, especially during intra-operative mapping, and patient discomfort (i.e., headache, fatigue) frequently restrict the number of tasks typically employed. Language tasks utilized among epilepsy surgery centers vary widely, although visual object naming is the most commonly used language task for ESM (approximately 60%) (Hamberger, Williams, & Schevon, 2014). Other language tasks utilized include auditory description naming, reading, and modified forms of the Token Test (for comprehension) (Boatman, Lesser, & Gordon, 1995; Hamberger, Goodman, Perrine, & Tamny, 2001; Luders et al., 1986; Malow et al., 1996; Ojemann, 1983a, 1990; Schwartz, Devinsky, Doyle, & Perrine, 1999).

Because it is invasive, ESM studies are limited to the areas considered relevant to the clinical situation, so that only the areas considered likely to be involved in seizure onset and spread will receive electrode coverage. As such, no normative data are available for ESM, and it remains unknown where ESM-based language areas would be found in healthy individuals. Although such information would be useful heuristically, it is not critical to the procedure's clinical utility, as stimulation-induced language errors are typically sufficient to infer an important functional role of the region stimulated. Further, it is generally assumed that if ESM could be performed in healthy individuals, positive language areas would mimic the areas associated with aphasia in stroke patients (i.e., a classic anterior/Broca's and posterior/Wernicke's pattern). There is some evidence that late-onset (i.e., >10 years of age) epilepsy patients might serve as a reasonable model of normative ESM patterns, as by age 10, "normal" language organization would likely already be established (Kadis et al., 2011). However, it could also be argued that abnormal EEG discharges or other neurological abnormalities present early in life, yet preceding clinical seizures could have interfered with normal language representation (Devinsky et al., 2000).

Finally, it is important to consider that, whereas language is complex, likely involving collaboration of multiple brain areas, ESM enables investigation of only small cortical areas, for only a short period of time. Similarly, although it might be tempting to attribute the function disrupted directly to the brain tissue stimulated, it can only be stated that inactivation of the stimulated area disrupted the particular function; however, this area may be part of a larger, integrated network. In this way, functional imaging (discussed later) may offer complementary data to ESM.

Certainly, the advantages of ESM are its high level of precision, and as a disruptive technique, the ability to identify brain areas that are *necessary* for language, not merely areas that might participate in ancillary fashion in language functioning. Nevertheless, these advantages should be considered together with limitations when interpreting ESM language results. With these cautions in mind, ESM-based findings related to language plasticity in epilepsy are presented in the following sections.

Influence of Patient-Related Characteristics

ESM studies in epilepsy patients have revealed two main alterations from the traditional left hemisphere, anterior (Broca's) and posterior (Wernicke's) language areas that would be expected in the normal population: (1) positive sites including, yet extending beyond, traditional language areas; and (2) positive sites adjacent or repositioned within the left hemisphere. Due to the invasive nature of ESM, the procedure is essentially always performed only unilaterally; we are aware of no published studies of bilateral ESM within the same patient. Although ESM results have been reported for the right hemisphere in patients whose pre-surgical evaluation revealed right-hemisphere involvement in language (Duchowny et al., 1996; Jabbour, Hempel, Gates, Zhang, & Risse, 2005), ESM cannot contribute significantly to the study of full versus partial transfer of positive areas to the right hemisphere. This area of study is better served via bilateral Wada testing and noninvasive neuroimaging.

The first pattern, characterized by an overall greater number and more diffuse spatial representation of positive language sites throughout the left hemisphere, tends to occur in "disadvantaged" groups. For example, Devinsky et al. (Devinsky, Perrine, Llinas, Luciano, & Dogali, 1993) and Hamberger et al. (Hamberger, McClelland, Williams, Goodman, & McKhann, 2007) reported relatively widespread distribution of naming sites in patients with earlier age of seizure onset (Figure 13.1). This pattern was also more likely to be found in patients with lower IQ scores, whereas patients with higher IQ scores tended to have naming sites limited to classic language areas (Devinsky et al., 2000; Ojemann & Whitaker, 1978). In a sample of left (dominant) epilepsy patients ranging in age from 19 to 64 years, Hamberger and colleagues (Hamberger, Williams, McKhann II, & Schevon, 2012) found that older patients had more diffuse spatial representation of visual naming sites, and a greater number of auditory description naming

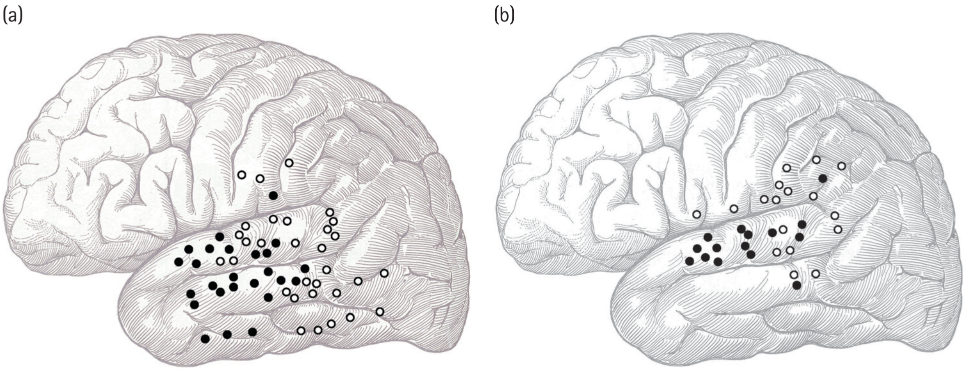

FIGURE 13.1. Topographic distribution of auditory (*solid circles*) and visual (*open circles*) naming sites in nonlesional epilepsy patients (A) and patients with space occupying temporal lobe lesions (B).

Source: Hamberger et al., *Epilepsia* (2007).

sites relative to younger patients. This might reflect a type of compensatory reorganization in which a greater amount of brain tissue is needed to support naming function. Interestingly, despite age differences in naming sites, there were no age-related differences in naming performance.

Consistent with these findings, Devinsky et al. (2000) reported atypical left-hemisphere language organization, characterized by naming and reading sites in anterior or inferior temporal cortex, in TLE patients with lower education levels, and poorer verbal memory and fluency scores. This contrasted with the more typical left-hemisphere organization limited to the posterior superior temporal gyrus (STG) (classic Wernicke's area) observed in TLE patients with higher education and stronger verbal performances (Devinsky et al., 2000; Hamberger, 2007).

Greater diffusivity of language cortex and even "atypical" language patterns associated with clinical features differ from the type of reorganization that appears to be more directly related to focal cerebral insult. In epilepsy, these generally include electrophysiological disruption and developmental abnormalities such as dysplasia, as well as more typical, space-occupying lesions. For example, Haglund et al. (Haglund, Berger, Shamseldin, Lettich, & Ojemann, 1994) found that epilepsy patients with left temporal lobe gliomas had proportionally fewer STG naming sites compared to similar patients without lesions, suggesting that the lesions either displaced or destroyed language sites that would ordinarily reside there.

In an ESM study comparing TLE patients with HS and without structural pathology, Hamberger, Seidel, and colleagues (2007) found proportionally fewer naming sites in anterior temporal cortex in HS patients relative to non-HS patients (consistent with their lower risk of naming decline following anterior temporal resection for seizure control) and that overall, auditory description naming sites in the HS patients were distributed more posteriorly relative to that in TLE patients without structural pathology (Hamberger, Seidel, et al., 2007). These results were interpreted to reflect intra-hemispheric reorganization of language in response to the likely, early development of HS. The posterior displacement of auditory-description naming sites was considered a possible result of the anterior temporal propagation of seizures and epileptiform discharges in TLE (Emerson, Turner, Pedley, Walczak, & Forgione, 1995).

As noted earlier, results from several Wada studies suggest that early onset left-hemisphere epilepsy often induces language transfer to the right hemisphere. Nevertheless, using ESM in both left- and right-hemisphere epilepsy patients, Duchowny and colleagues found language sites remaining within the left hemisphere, often adjacent to, and sometimes overlapping with, developmental lesions and epileptogenic regions, even in patients with epilepsy onset prior to age 5 years (Duchowny et al., 1996). Right-hemisphere language was rare, found only in patients with very large, early lesions acquired before age 5 that had clearly destroyed language-relevant cortical areas.

Right-Hemisphere ESM

As ESM is generally performed only in the hemisphere considered dominant for language, ESM data are inherently biased, and little is known regarding ESM language testing in the non-dominant hemisphere. In a unique study by Wyllie and colleagues (Wyllie et al., 1990), 15/15 patients who were left-hemisphere language dominant on Wada testing showed no evidence of right-hemisphere language using ESM. However, 2/7 patients who were shown to be right-hemisphere language dominant on Wada testing had language sites identified in the left hemisphere with ESM. This suggests the possibility of incomplete transfer of language to the right hemisphere, and highlights that the left-hemisphere language contribution was not detected with Wada testing (Wyllie et al., 1990). Using ESM in patients determined to have bilateral language representation, Jabbour and colleagues found frontal and/or temporal language areas analogous to the classic essential language areas of the dominant left hemisphere in 4/6 patients identified with left-sided ESM (Jabbour et al., 2005).

As noted, one shortcoming of ESM is that the procedure enables investigation of only small cortical areas on a given stimulation trial, using relatively simplified tasks, due to the time constraints associated with administration of an electrical current to the brain. Human language is complex, involving integration and coordination of multiple brain regions, including sulcal and subcortical brain areas that are not accessible to ESM. As described in the following, neuroimaging techniques are not constrained in these ways, thereby offering other, or possibly complementary information to ESM findings.

INTER- AND INTRA-HEMISPHERIC REORGANIZATION: EVIDENCE FROM fMRI

In recent years, “activation techniques” have been used increasingly to measure changes in brain function during performance of language-related tasks, allowing for in vivo or real-time detection of regions that are presumed to be involved in the task at hand. One promising method is fMRI, which extends beyond the traditional structural technology of MRI by measuring hemodynamic changes (e.g., increased blood flow to local vasculature) that are assumed to accompany neural activity in that specific area (for more details regarding technical aspects of fMRI, see Heim & Specht, Chapter 4 in this volume; Belliveau et al., 1990; Ogawa et al., 1993; Tank, Ogawa, & Ugurbil, 1992; Turner, Le Bihan, Moonen, Despres, & Frank, 1991). As fMRI is noninvasive, it can be used repeatedly with minimal time restrictions, and with both patients and healthy control subjects due to minimal, if any, health risks. Also, and perhaps more important, it provides detailed information about changes in activation both within and across cerebral hemispheres, thereby providing useful information regarding language lateralization and localization at the same time. This is particularly relevant, as language representation is not a purely unilateral phenomenon (see Van der Haegen & Cai, Chapter 34 in this volume; Springer et al. 1999).

Supporting the use of fMRI as a valid alternative for language *lateralization*, a number of studies have demonstrated high concordance rates with the Wada procedure (Benke et al., 2006; Binder et al., 1996; Rutten, van Rijen, van Veelen, & Ramsey, 1999; Woermann et al., 2003), although it also has been shown that the level of congruence varies significantly depending on the specific methods and protocols utilized (Balsamo & Gaillard, 2002; Benson et al., 1999; Lehericy et al., 2000). The use of fMRI for language *localization* has also been bolstered by several studies showing good concordance rates with ESM (Carpentier et al., 2001; FitzGerald et al., 1997; Pouratian, Bookheimer, Rex, Martin, & Toga, 2002; Ruge et al., 1999), although another study rightly pointed out that caution must be exercised when using the information for surgical decisions because the techniques were not perfectly correlated (Roux et al., 2003).

A number of fMRI studies have added critical knowledge to our understanding of language-related substrates in epilepsy. It is well known that patients with epilepsy have a higher incidence of atypical language representation than the general population (Rasmussen & Milner, 1977; Springer et al., 1999). Not surprisingly, in a retrospective analysis comparing a mixed sample of pediatric epilepsy patients with healthy controls, Yuan and colleagues (2006) found a higher rate of atypical language lateralization in the patient group. In addition, based on prior evidence that increased specialization toward the left hemisphere is a function of normal development (Holland et al., 2001; Schapiro et al., 2004; Szaflarski, Holland, Schmithorst, & Byars, 2006), they showed a near significant association between age and language lateralization in the control group (implying a trend that may have been obscured by small sample size), yet no significant association in the patient group, suggesting that epilepsy can either disrupt the normal developmental convergence toward left-hemisphere language areas and/or lead to the activation or establishment of compensatory areas in the right hemisphere.

The propensity for inter-hemispheric reorganization has been demonstrated in a number of fMRI studies. For example, similar to other investigators who have demonstrated right-hemisphere language activation in left-sided seizure patients (Berl et al., 2005; Brazdil, Zakopcan, Kuba, Fanfrdlova, & Rektor, 2003; Janszky, Jokeit, et al., 2003; Rosenberger et al., 2009), Adcock and colleagues (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003) used an auditory-based word decision to explore activation asymmetries in Broca's and Wernicke's areas in patients with left-hemisphere seizure foci compared to normal control subjects. As expected, the patients were more likely to have right-sided activation overall. Furthermore, when the investigators specifically looked at patients with right-hemisphere activation, the identified sites were right-sided homologues of Broca's and broadly defined Wernicke's areas. However, patients who remained left-dominant showed only slight and variable differences from the control group within the left mid-temporal gyrus, indicating only minimal intra-hemispheric reorganization among these patients.

In another compelling study, Janszky and colleagues (2006) compared patients with left and right MTLE to investigate whether frequent left-sided interictal abnormalities (i.e., spikes or sharp waves) would induce a shift in language functioning to the right hemisphere. Using a covert word-generation task and calculated activation asymmetry indices, they indeed found a higher incidence of atypical language representation among the left MTLE group compared to the right MTLE group. Most interesting, within the left MTLE group only, a higher frequency of interictal abnormalities was associated with greater left-to-right shift of language functioning. Importantly, this shift was not influenced by other variables, including gender, age, age of epilepsy onset, seizure frequency, IQ, or verbal fluency, leading the investigators to conclude that chronic and frequent interictal abnormalities might represent a primary influence in inter-hemispheric language reorganization independently of other factors.

It is important to note that fMRI research does not always suggest a complete shift of language from the left to the right hemisphere among patients with left-sided seizures. For instance, Brazdil et al. (2005) studied right-handed patients with unilateral left TLE (including suspected medial onset and documented hippocampal sclerosis) versus a healthy control sample. Using a silent word-generation task, they showed significantly greater bi-hemispheric representation in the patient group. Furthermore, while activation patterns among controls generally corresponded with known language circuits, the patients showed less consistent and more widespread changes in both hemispheres, including a lack of activation in traditional Broca's area, with greater activation in the left medial frontal gyrus extending into the right anterior cingulate gyrus, as well as the right inferior frontal gyrus. Other clear differences from controls were also noted in the anterior cingulate, basal ganglia, and cerebellum, but these did not reach the level of statistical significance. The authors concluded that language does not simply shift from one hemisphere to the other; rather, there is a very complex and highly individualized pattern of reorganization involving both inter- and intra-hemispheric changes in neuronal networks.

In related research by Mbwana and colleagues (2009), control participants again demonstrated primary activation in known language areas. However, language activation patterns were much less consistent among a heterogeneous group of patients with left-hemisphere seizure foci, resulting in the identification of several subgroups, as follows: group 1a (predominant left-sided activation with a significant cluster in the left posterior superior temporal sulcus); group 1b (predominant left-sided activation with no significant difference from the control group); group 2a (predominant right-sided activation with significant clusters in the right inferior middle superior frontal gyri, middle temporal gyrus, right cingulate, and left cerebellum); and group 2b (predominant right-sided activation in the right inferior middle superior frontal gyri, right angular gyrus, and left cerebellum). The results were interpreted as showing tendencies for both intra-hemispheric reorganization (i.e., compensation by ipsilateral adjacent regions as seen in group 1a) and inter-hemispheric reorganization (i.e., recruitment of contralateral homologous regions as seen in groups 2a and 2b) among individuals with left-hemisphere seizure disorders. With the exceptions of handedness and MRI detected pathology, other factors such as gender, age, age of onset, indications of early insult, duration of seizures, and location of seizure focus were not significantly different between left- and right-lateralized patients, highlighting the importance of investigating language patterns on an individual basis.

With respect to symptomatic epilepsy (i.e., seizures associated with known structural lesions), the location of the lesion(s) can have significant bearing on language organization, although results are not always predictable. To illustrate, Liegeois and colleagues (2004) used fMRI to study children and adolescents with lesions that were either adjacent to or within anterior language cortex (i.e., Broca's area) or lesions that were remote from traditional language sites (i.e., hippocampus, parahippocampus, temporal pole), compared to healthy controls (see Figure 13.2). Not surprisingly, the patients had a higher rate of atypical language lateralization (50% left-, 10% bilateral-, 40% right-dominant). However, inconsistent with previous reports in the literature (Devinsky et al., 1993; Isaacs, Christie, Vargha-Khadem, & Mishkin, 1996; Lazar et al., 2000; Rasmussen & Milner, 1977), lesions near traditional language areas did not result in higher inter-hemispheric reorganization, as 80% of patients with lesions near Broca's area remained left-hemisphere dominant, whereas 80% of patients with lesions away from traditional language areas had bilateral or right-sided dominance. Importantly, other clinical factors such as handedness, EEG abnormalities in the left frontal lobe or

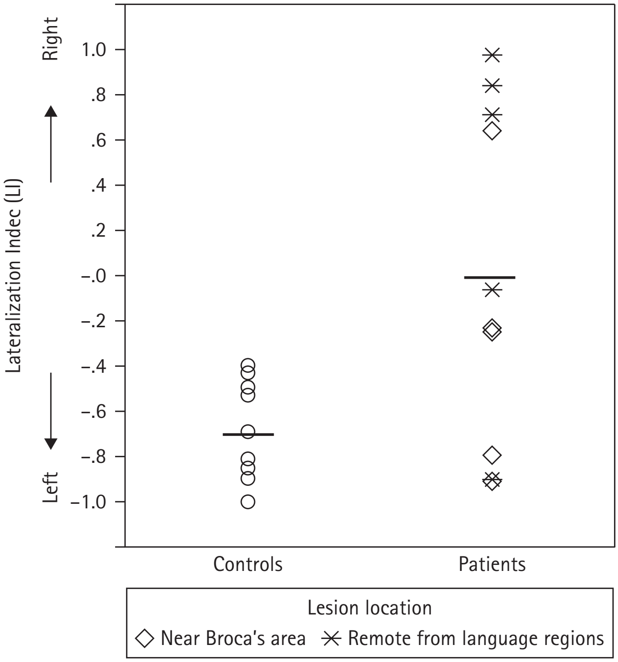

FIGURE 13.2. fMRI lateralization index (LI) in control participants and patients. Bars indicate group means.

Source: Liegeois et al., *Brain* (2004).

right hemisphere, early onset of chronic epilepsy, and age at first seizure did not appear to have any bearing on language lateralization.

In similar fMRI research, Weber and colleagues (2006) demonstrated that patients with left hippocampal sclerosis were more likely to have atypical language lateralization than patients with left frontal or left temporal (lateral) lesions, and that the latter patient groups displayed similar left-sided activation patterns compared to control participants. The results suggested that the left hippocampus may be important in determining language dominance, although it is structurally remote from so-called language eloquent areas. One possible explanation is that damage prior to or during language acquisition can induce a shift toward the right hippocampus for the development of lexical, semantic, and learning of grammatical rules, with subsequent involvement of the right neocortex through reciprocal connections with the medial temporal region.

The studies reviewed here are intended as a brief yet representative sampling of the growing body of literature on fMRI and language organization in epilepsy. Despite the clear advantages of using fMRI for this purpose, one of the major shortcomings of this technique is that specific functions might be difficult to isolate (e.g., language tasks might also activate areas associated with auditory processing and sustained attention), and careful research methods are therefore needed to rule out extraneous factors when interpreting the results. It is also assumed that any underlying pathology has not disrupted hemodynamic activity in the regions of interest or expected activation. Finally, as with any other mode of investigation, differences in methodology between studies are bound to yield different results. Nevertheless, it seems fairly clear that language organization and reorganization in epilepsy is a very complex and heterogeneous process, and that further exploration is warranted to better our understanding and improve the clinical utility of this technique.

Epilepsy Surgery and Language Reorganization

As noted earlier, chronic and medically refractory seizure disorders often lead to elective surgery, which, unlike unexpected neurological conditions (e.g., traumatic brain injury, stroke), allows for careful pre- and postoperative evaluation of language functions. When considering language reorganization, this is of vital importance because potential changes can be measured objectively in a controlled fashion, rather than simply inferred retrospectively. An ideal situation for demonstrating true language plasticity would involve persons with established language networks/abilities prior to neurological illness and surgery and verifiable changes in those networks/abilities afterward. A number of case examples and patient series are presented in the following, which provide compelling evidence of both functional and structural alterations, with implications for the malleability of language circuits in the brain.

In keeping with the fMRI research reviewed in the preceding section, Hertz-Pannier and colleagues presented a case report of a boy who developed intractable epilepsy related to Rasmussen's syndrome at age 5 years and 6 months and who later underwent a left hemispherotomy (e.g., complete disconnection but not removal of the left hemisphere) at age 9 years, after previously normal and complete language acquisition (Hertz-Pannier et al., 2002). This provided a unique opportunity to compare fMRI studies from both before and after his surgery. The preoperative fMRI (obtained at age 6 years and 10 months) reportedly showed left lateralization during a covert semantic word-generation task. By contrast, the postoperative fMRI (obtained at age 10 years and 6 months) reportedly showed right-sided activation during word-generation, sentence-generation, and story-listening tasks. Most important, it was reported that the latter activation was "seen mainly in regions that could not be detected preoperatively, but mirrored those previously found in the left hemisphere (inferior frontal, temporal, and parietal cortex), suggesting reorganization in a pre-existing bilateral network" (Hertz-Pannier et al., 2002, p. 361). It was concluded that this de novo activation provided longitudinal evidence that the boy's previously nondominant right hemisphere was capable of sustaining late plasticity changes for language, although it is important to note that his receptive language functions recovered more quickly than his expressive language functions, which were still quite limited compared to healthy peers at the last time he was tested (e.g., verbal fluency = −2 SD, naming = −3 SD).

A number of other reports have also challenged the traditional belief that the critical period for language acquisition ends around 6 years of age (see Marcotte & Morere, 1990; Woods & Carey, 1979; Woods & Teuber, 1978). In one case, Telfeian et al. (Telfeian, Berqvist, Danielak, Simon, & Duhaime, 2002) described a female patient with seizures secondary to Rasmussen's syndrome beginning at age 11 who underwent a dominant hemispherectomy at age 16. Despite progressive language deterioration before the surgery and severe global aphasia immediately after surgery, she subsequently demonstrated a remarkable recovery of language functions over time. Specifically, performance on the Western Aphasia Battery 1 and 2 years after surgery showed improvements of 600% in spontaneous speech, 9% in comprehension, 45% in repetition, 27% in naming, and 89% in the aphasia quotient. Not citing neural plasticity per se, the authors speculated that this recovery was due primarily to the interruption of a disease process, allowing the unmasking of right-hemisphere functions that had been suppressed by diffuse seizure activity. However, they particularly emphasized the point that language recovery is very much possible, even in adolescence after a late-onset disease process.

In another case report, Voets and colleagues performed fMRI studies on a patient with Rasmussen's encephalitis diagnosed at age 6 both before and after surgical removal of the left hemisphere at age 14 (Voets et al., 2006). Using phonemic and semantic fluency tasks, the preoperative scan revealed an activation pattern involving primarily inferior frontal and superior temporal regions bilaterally, whereas postoperative activation was limited almost exclusively to the right inferior frontal gyrus (IFG). Importantly, mean word-generation scores were similar (average of 4 words in 30 seconds), indicating no real change in function as a result of the surgery. In addition, a more specific region of interest analysis showed that the peak preoperative activation in the right IFG was seen in the pars triangularis for letter fluency and just superior to the pars orbitalis for category fluency, but the peak activation patterns both shifted more medially and posteriorly in the frontal operculum/anterior insula postoperatively. The findings were interpreted as longitudinal evidence of relative changes in localization of activation in the right IFG after left hemispherectomy.

In yet another case of late-onset language development, though involving a different underlying pathology, Vargha-Khadem and colleagues described a boy with Sturge-Weber syndrome and related mutism, who suddenly began to develop speech at age 9 years and 5 months, 10 months after left hemidecortication and withdrawal of anticonvulsant medications (Vargha-Khadem et al., 1997). He subsequently displayed a significant improvement in verbal communication, with increasing mean length of utterance from 0 to 11.6 words over the next 13 months, eventually reaching the normal range for his age on tests of English morphology and phonological imitation of multisyllabic words. Based on this remarkable case, the authors concluded that the complex neural systems underpinning speech can remain viable even if unused for the first 9+ years of life, and that clearly articulated and well-structured language functions can then be developed entirely within an isolated right hemisphere.

Similar descriptions of language reorganization have been reported in adolescents with Rasmussen's encephalitis using intracarotid amobarbital testing (IAT) (Loddenkemper, Wyllie, Lardizabal, Stanford, & Bingaman, 2003) and others with intractable epilepsy and surgical resection using magnetoencephalography (MEG) (Papanicolaou et al., 2001). Further, there is growing evidence that patients can develop essentially normal language functioning after left hemispherectomy (Devlin et al., 2003; Vining et al., 1997). The possibility of postoperative language development or recovery is critical with respect to the catastrophic epilepsies that require radical surgical procedures such as hemispherectomy. Hopefully, further research will shed light on the circumstances/conditions that promote the likelihood of this phenomenon.

EVIDENCE OF STRUCTURAL CHANGE IN LANGUAGE CIRCUITS AFTER EPILEPSY SURGERY

Moving beyond reported changes in language activation measured by fMRI BOLD signal, a newer line of inquiry has also shown important structural changes measured by diffusion tensor imaging (DTI) (see Catani & Forkel, Chapter 9 in this volume) that occur after neurological surgery involving language network areas. In one such study, Schoene-Bake and colleagues used postoperative DTI to demonstrate that epilepsy patients with left or right hippocampal sclerosis exhibit widespread degradation of fractional anisotropy (FA; a measure of fiber density, axonal diameter, and myelination in the white matter) in main fiber tracts that are not limited to the temporal lobe—including uncinate fasciculus, fronto-occipital fasciculus, superior longitudinal fasciculus, corpus callosum, and corticospinal tract in the surgical hemisphere—and that these changes seem to be more extensive in patients who undergo left-sided surgery (Schoene-Bake et al., 2009). Although pre-surgical data were not available for direct comparison, it was inferred from comparisons with other published data that both epilepsy and surgery can lead to neuronal loss, as fiber tracts undergo a process of Wallerian degeneration when they are disconnected from afferent and/or efferent structures.

Building on this idea, Yogarajah and colleagues carried out a longitudinal study of left and right TLE patients also using tractography (Yogarajah et al., 2010). Pre- and post-surgical comparison revealed widespread and significant (mean 7%) reductions in fractional anisotropy in white matter networks connected to the area of resection in both groups. At the same time, they also observed a widespread (mean 8%) increase in fractional anisotropy after left anterior temporal lobe resection in the ipsilateral external capsule and posterior limb of the internal capsule, and corona radiata, believed to represent a ventro-medial language network. Moreover, these morphometric findings were correlated with changes in verbal fluency after resective surgery, in that larger increases in parallel diffusivity (a measure of diffusion along the fiber axis) were associated with smaller declines in language proficiency. The authors concluded that this ventro-medial network represented structural reorganization in response to the anterior temporal lobe resection, which tends to cause greater damage in the more susceptible dorsolateral language pathway.

CONCLUDING REMARKS

In summary, research in epilepsy has undoubtedly made significant contributions to the understanding of language organization and plasticity. In this chapter, we have reviewed relevant findings from disruption (e.g., Wada, ESM) and activation methods (e.g., fMRI), as well as more recent advances in structural imaging (e.g., DTI), all of which have enhanced our knowledge about this incredibly complex phenomenon. One clear message is that, despite an ever-improving theoretical understanding regarding both functional and structural anomalies that can influence brain-language relations at varying points in development, recent findings have challenged previously held beliefs arguing against neural plasticity with increasing age, and demonstrated that the clinical presentation of language is quite heterogeneous among patients with epilepsy, thereby underscoring the practical importance of using available techniques on a case-by-case basis to optimize patient outcomes. The study of language in epilepsy is very much a burgeoning field of inquiry, and more refined research paradigms, together with ongoing improvements in technology, promise continued advancement of our knowledge regarding the neuroscience of language organization and reorganization.

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CHAPTER 14

LANGUAGE DEVELOPMENT IN DEAF CHILDREN

Sign Language and Cochlear Implants

AARON J. NEWMAN

INTRODUCTION

DEAFNESS and other forms of hearing loss represent the fifth leading cause of disability in the world; the 2013 Global Burdens of Disease study (Vos et al., 2015) estimated the total prevalence of hearing loss worldwide at over 1.2 billion people, with over 400 million people—over 5% of the world's population—having moderate or greater loss (defined as a reduction in thresholds of 35 dB or greater, the level at which hearing loss is considered "disabling"). In the United States, it is estimated that 2–3 out of every 1,000 children are born with detectable hearing loss in one or both ears, and hearing loss is one of the three most common congenital disorders (Vohr, 2003). The prevalence of hearing loss is higher in other parts of the world, with highest incidence in South Asia, Asia Pacific, and Sub-Saharan Africa (Vos et al., 2015).

The consequences of hearing loss can be quite severe. Because language is used both in education and for self-regulation ("self-talk"), children with hearing loss are more likely to have delays in language development, reading, and social development, as well as behavioral problems—especially if they do not have the opportunity to learn and use sign language, or to have their hearing restored. The consequences of this can be far-reaching and lifelong: on average, deaf people have lower levels of educational attainment, lower incomes, less likelihood of holding a managerial or professional occupation (even when adjusted for education level), and report lower levels of job satisfaction, along with higher incidences of work stress and depression (Rydberg, Gellerstedt, & Danermark, 2009; Shein, 2003). People who become deaf as adults suffer language comprehension difficulties, difficulties in normal activities of daily living, participation restriction, social isolation, and high rates of depression.

Clinically, “deafness” can be defined as moderate (40–60 dB loss), severe (60–80 dB), and profound (>80 db) hearing loss. In practice, these different levels are distinguished clinically because they affect activities of daily living to different degrees, and have different standards of treatment. People with moderate or severe impairment are generally still able to detect environmental noises, and are at least aware of speech. However, even with moderate loss, speech perception can be challenging, and worse in environments with background noise (such as outside, in a room with multiple people talking, or with background music, radio, TV, etc.). With severe impairment, speech perception may be difficult or impossible, even under ideal listening conditions. It is important to recognize as well that hearing loss is often asymmetric (worse in one ear); generally the rating of severity of loss is based on the better ear, but one can expect worse functional hearing in someone with profound loss in one ear and moderate in the other, compared to someone with moderate loss in both ears.

Numerous options are available for persons with hearing loss, including learning and using sign language, hearing aids, and cochlear implants (CIs). Hearing aids are devices that sit on or around the ear and amplify incoming sounds. In contrast, CIs involve a device that is implanted in the base of the skull, with a wire that is threaded into the cochlea (see Figure 14.1). A microphone attaches to the outside of the head via a magnet, and transmits sound across the skull to the CI, which then stimulates the cochlea via electrodes on the inserted wire. CIs take advantage of the place-coding organization of the cochlea, whereby different auditory frequencies are received through electrical stimulation at different points along the cochlea. These rehabilitative options are not mutually exclusive; for example, many deaf people have hearing aids or CIs, and CI users may have a CI on one side and a hearing aid on the other. Profoundly deaf children are routinely referred for cochlear implantation, and in most cases this is effective in bringing hearing into the normal range. However, even with hearing restored to audiologically “normal” levels, many children with CIs show functional deficits (e.g., speech perception in noisy environments; reading) that persist into adulthood. As well, these treatment options have been the subject of significant debate in cultural, educational, and health-care spheres. Although these debates encompass arguments on both empirical and cultural grounds, a solid understanding of how deafness affects brain organization and language abilities is central to better understanding how society can best address the needs of people with severe hearing loss.

This chapter is focused on language development in deaf children, with a particular emphasis on children who use CIs and the factors that influence language outcomes. After briefly reviewing sign language (see also Corina & Lawyer, Chapter 16 in this volume), we first consider the effects of auditory deprivation on neurodevelopment, followed by a description of language outcomes in deaf children. This will be followed by a review of the neuroimaging literature on neuroplastic reorganization in deafness and after hearing restoration. We then discuss the major predictors of language outcomes in children with CIs. The chapter concludes with a summary and recommendations for practice and future research.

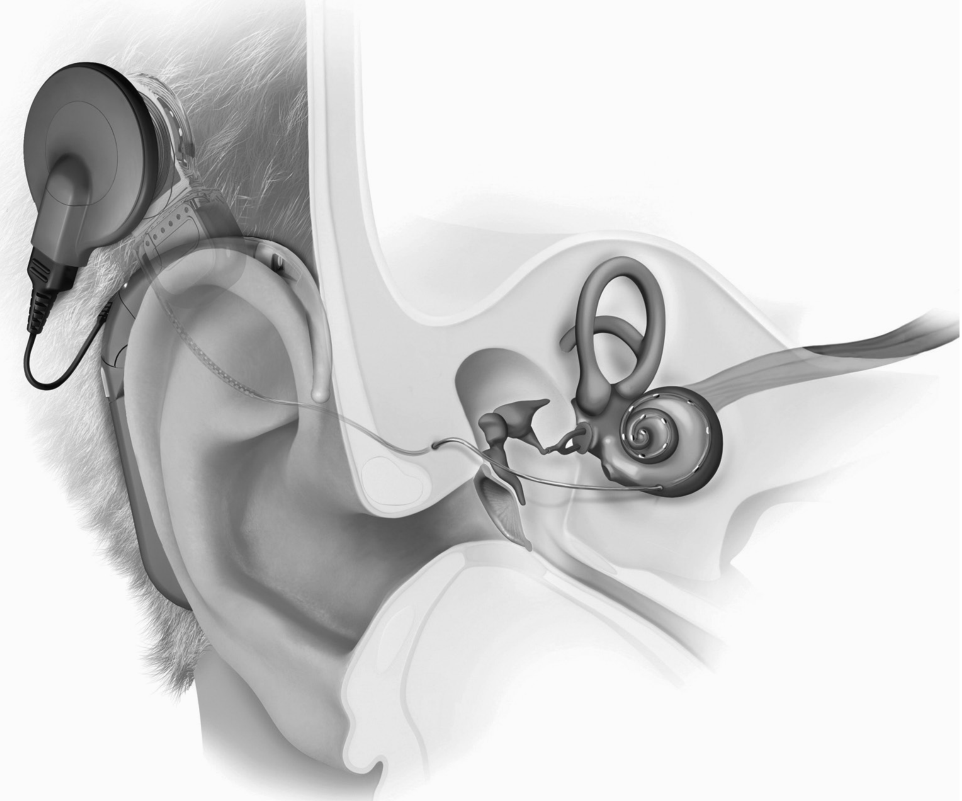

FIGURE 14.1. A cochlear implant. The external microphone unit is shown in the top left, and includes a piece that fits over the external part of the ear, as well as a magnetic transmitter that connects to the implanted unit. The implant itself is shown above and behind the ear, partially occluded by the external magnet. Running from the implant is a wire that is threaded into the cochlea (shell-shaped structure in the center-right of the figure) and turns sound input into electrical stimulation to the cochlea. Signals are then conducted via the auditory nerve (right side of figure) to the brain.

Source: Image courtesy of MED-EL.

SIGN LANGUAGE AND DEAF CULTURE

Throughout the world, natural sign languages—which have all the linguistic complexity and characteristics of spoken languages—have evolved naturally among communities of deaf people. Deaf children exposed to sign language from birth develop normal language abilities, and indeed children who learn sign language from birth later show far greater mastery of spoken language (oral and written) than deaf children not exposed to sign or exposed only later in life (Mayberry, Lock, & Kazmi, 2002). However, only an estimated 4%–5% of congenitally deaf children are born to deaf parents, and so unfortunately the majority of deaf children do not have a fluent signing parent from whom to learn a sign language. Although parents can of course begin to learn sign language and use it with their children, this is a significant undertaking for any parent of a newborn—and in general cannot be expected to provide the child with optimal, fluent early language input.

One very important thing to recognize is that the term "sign language" actually encompasses a variety of manual communication systems, which are very different in their origins, linguistic status, and the situations and cultures in which they are used. In the preceding paragraph, the term "*natural* sign languages" was used, very intentionally, to describe visual-manual languages that have evolved independently of each other in Deaf communities around the world. Contrary to popular misunderstanding, there is no universally intelligible sign language—just like spoken languages, independent communities of people have developed their own sign languages that differ from each other in their phonological structure, grammar, and form-to-meaning mappings (i.e., vocabulary). Because sign languages have evolved within communities of deaf users, they are not visual-manual versions of the spoken languages used in the same geographic locations. For example, American Sign Language (ASL), which is used by the Deaf community throughout the United States and Canada, has many syntactic differences from spoken English. Attempting to literally translate an English sentence into ASL will produce a sentence that may well violate ASL's syntactic rules; many words and morphemes that are required in English are not required in ASL (and may actually not have an ASL equivalent), or are required in different sentence contexts. Further underscoring the distinction between signed languages and the spoken languages used in the surrounding hearing communities is the fact that although English is the primary spoken language in the United States, Australia, Ireland, and the United Kingdom, each of these countries has its own, linguistically distinct sign language. For example, British Sign Language (BSL) is mutually unintelligible with ASL; ASL is derived from *langue des signes française* (LSF; French Sign Language), not BSL. In spite of their having evolved largely independently of one another, all natural sign languages appear to follow some universal principles. Some of these are universal principles of human language that cross spoken and signed forms (such as having a limited phonological inventory and phonotactic rules; having hierarchical and recursive syntactic structure), while others are unique to sign language but common across sign languages (for example, the phonetic inventories of sign languages are defined based on the parameters of handshape, orientation, location, and movement; syntactic morphemes are produced simultaneously with their root, rather than sequentially).

In contrast to natural sign languages, a variety of *auxiliary* sign languages, or manually coded languages (MCL), have been developed by hearing educators in efforts to help provide deaf people with access to spoken languages. Generally speaking, these are ways of representing a spoken language manually—so the vocabulary, word order, and syntactic morphemes of a spoken language are given manual equivalents. MCLs are often used in deaf education settings (and parents of deaf children are encouraged to use them) specifically because they offer access to the spoken language of the milieu. The assumption underlying their use is that by having visual-manual access to the spoken language, the child will have an awareness and understanding of that language and its associated phonological and morpho-syntactic systems, which will in turn facilitate tasks such as learning to read and, if a CI is provided, learning to hear and understand the spoken language.

Language is a defining aspect of many cultures, and this is certainly true of sign languages: there is a widely recognized distinction between deafness (profound hearing loss) and Deaf culture (spelled with a capital "D"). Deaf culture revolves around a shared (signed) language, but encompasses more than just language (including shared beliefs, values, traditions, and arts) and includes both deaf and hearing people who sign. Within Deaf culture, hearing loss is not considered a medical condition, and Deaf people—more than most other groups of people who have a condition defined by the medical community—tend to resent views of deafness that center around concepts of deficits, impairment, or disability. Rather, hearing loss is viewed as a central aspect of cultural identity (although many hearing signers are part of Deaf culture as well). The notion that deafness needs to be treated, or "fixed," is viewed as a threat to an individual's identity and to Deaf culture more generally. Cochlear implants were thus not initially welcomed by most of the Deaf community, but rather were viewed as a significant threat, and even an attempted act of "cultural genocide" by mainstream culture.

Sign Language Development

An immense amount of linguistic development occurs in the first year of life, going from tuning children's brains to the phonemic inventory of their native language, through becoming able to segment the incoming, continuous speech stream into words, to comprehending and understanding first words. Deaf infants exposed to fluent signing from birth show similar developmental milestones, at similar ages, to their normally hearing peers (Petitto et al., 2001). For example, they begin canonical babbling (using native language phonemes) at the same age (7 months) as hearing babies (Petitto & Marentette, 1991), and show increasing sensitivity to, and mastery of, ASL phonological structure over the course of development (Marentette & Mayberry, 2000). Deaf babies generally produce their first signs some months earlier than hearing children, which has been attributed to more rapid development of motor control of the hands than the vocal articulators. As adults, extensive neuropsychological and neuroimaging data demonstrate that in the deaf, native sign languages activate the same classical, left-lateralized brain regions as spoken languages (see Corina & Lawyer, Chapter 16 in this volume). Together with the developmental data, these findings emphasize the fact that signed and spoken languages are linguistically and neurologically equivalent, and that native signers are at no linguistic disadvantage in their native language compared to native learners of a spoken language.

Some of the strongest evidence in favor of sensitive periods in L1 development comes from studies of deaf people who learned a natural sign language at different ages (such cases are more prevalent among deaf people due to great variability in how deaf children were historically educated). On numerous tests, including grammatical judgment, complex grammatical morphology, and sentence recall, there was a clear gradient whereby native ASL learners outperformed later learners, and those who learned as young children outperformed those who only began L1 acquisition after age 12 (Mayberry, 1993; Newport, 1990). Notably, in all of these studies the participants were tested as adults and so all had many years of ASL signing experience, confirming that even delays of a few years in L1 exposure cannot be overcome by years of subsequent practice. Mayberry and colleagues have further demonstrated that these linguistic deficits in late L1 acquisition are mirrored by changes in brain organization for language. Examining adults who first learned ASL as their L1 between the ages of 0–14, they found linear declines in activation of left hemisphere frontal and temporal language areas with increasing age of acquisition (AoA), along with increased activation in occipital regions, which may have indicated greater effort required for processing the low-level (visual) features of signs at the expense of fluent linguistic processing (Mayberry, Chen, Witcher, & Klein, 2011a). Using another imaging technique, magnetoencephalography (MEG) (see Salmelin, Kujala and Liljeström, Chapter 6 in this volume), Ferjan Ramirez and colleagues (2013) similarly found unusual patterns of brain activity, involving occipital and parietal regions, in deaf signers who learned ASL after age 14.

This research confirms that delays in L1 exposure, as experienced by deaf people who do not receive signed language input from birth, lead to lifelong delays in L1 performance. Further evidence also indicates that such delays in signed L1 exposure have permanent impacts on spoken L2 learning. Mayberry and colleagues (2002) compared deaf native ASL signers with deaf people who first learned ASL between ages 9–15, and a group of hearing people who learned English as a second language at a range of ages matched to the ASL late learners (thus all groups had learned English late as their L2). On a test of English grammatical judgment, native ASL users performed comparably to hearing English L2 learners, and both groups performed significantly better than deaf late learners of ASL. In other words, poorer L2 performance was attributable to the lack of L1 learning, but—critically—not whether the L1 was spoken or signed, nor whether people were deaf or hearing. Mayberry and Lock (2003) extended these findings, showing that on both English grammatical judgment and sentence comprehension, native ASL signers and hearing English L2 learners performed comparably to each other, and not significantly worse than native English speakers. More recent work has extended these findings to deaf CI users. Hassanzadeh (2012) compared two groups of CI users, matched in age, duration of deafness, and age of implantation. The groups differed only in that one had deaf parents, and the other had hearing parents. Children of deaf parents outperformed those of hearing parents on spoken language comprehension and production at every time point tested, from 6 months to 10 years post-implantation. (Although the language use of the parents in this study was not explicitly reported, the author indicated that sign language was used, and speculated that more generally, deaf parents adopted communication strategies from birth that were heavily visual and accommodated children's lack of hearing.) A similar finding was reported by Sarant and colleagues (2001), who found that having a family history of hearing loss predicted significantly better preschool language skills in young CI users. Taking a slightly different tack, Davidson and colleagues (2014) compared spoken language outcomes between deaf CI users and hearing children, all of whom had ASL as their L1 by virtue of being born to deaf, signing families. The CI users' English perception and production skills on standardized tests were within (and in some cases even exceeded) age-appropriate norms and were indistinguishable from those of the hearing children. This was particularly notable because the deaf children had received their CIs after the age of 1 year (between 16–35 months of age; they had 1–4 years of experience with the CI) and so, on the basis of the literature reviewed earlier, would be expected to perform on average below hearing peers on these standardized tests.

Similar findings have been obtained in a number of studies investigating deaf people's reading abilities. Learning to read is obviously challenging for deaf people, since it normally involves mapping novel visual shapes (letters) to sounds (phonemes), which someone who is pre-lingually deaf has no experience with. On average, (non CI-using) deaf high school graduates read at a grade 3–4 level (Marschark et al., 2009). However, this statistic masks the fact that many deaf people do become skilled readers, with many succeeding in higher education and earning professional and doctoral degrees. Recent research has focused on what cognitive skills deaf people utilize in becoming successful readers (Marschark et al., 2009). A notable finding from these studies is that although phonological abilities (e.g., phonological awareness, phonological coding ability) are among the strongest predictors of reading ability in hearing people, they account for a much smaller proportion of variance in deaf readers (Holmer, Heimann, & Rudner, 2016; Mayberry, Del Giudice, & Lieberman, 2011b). This indicates that while lack of access to spoken language phonology may create a challenge for learning to read, it is not insurmountable, and skilled deaf readers develop alternative skills for fluent reading, perhaps focused more on visual processing and efficient, whole-word recognition. Most notably for the current discussion, several studies have found that signing abilities predict better reading abilities (T. E. Allen, 2015; Chamberlain & Mayberry, 2008; Freel et al., 2011); notably, Allen found this relationship to hold in signing families of both deaf and hearing children, but not in families of deaf children who only learned sign language later in childhood, outside of their family setting—again emphasizing the important role of learning a native language from birth. However, as Godin-Meadow and Mayberry (2001) note, sign language fluency does not guarantee good reading ability—reading ability is a specific skill that needs to be taught. An intriguing recent suggestion is the "functional equivalence" hypothesis (McQuarrie & Parrila, 2014): that exposure to a natural language with a phonetic structure—regardless of whether that language is spoken or signed—during sensitive periods for language development in infancy is essential for developing normal reading abilities.

Language Development with a Cochlear Implant

As noted in the introduction to this chapter, CIs are considered standard of care for children with severe hearing loss. Overall, the evidence overwhelmingly supports the efficacy of CIs to restore hearing. At the same time, many CI users perform below their normally hearing peers on standardized outcome measures, especially those related to language and scholastic performance—effects that can persist into high school and are thus not ameliorated simply by years of hearing experience. A significant factor contributing to heterogeneity of CI outcomes—but also providing useful information—is the fact that children may receive their implants at a wide variety of ages. There are several reasons for this. First, in the early days of cochlear implantation, surgeons (and practice guidelines) were more conservative and tended to wait until children were 3 or more years old prior to CI surgery. However, more recent evidence has suggested that infants not only tolerate CI surgery well, but that their outcomes tend to be better with earlier implantation. Even with this evidence, many parents and clinicians may choose to wait longer prior to the surgery; as well, some children are not born deaf but become so sometime during childhood. In other cases, limitations in health-care resources or insurance may preclude children from receiving CIs as early as might be desired. These variables result in "natural experiments" that have allowed researchers to study a range of variables that affect CI outcomes.

Most of the evidence concerning age of implantation comes from relatively young children, likely because of the increasing recognition that earlier implantation results in better outcomes, and because longitudinal research is more difficult, costly, and prone to dropouts. On both comprehension and production measures, several studies have shown better performance by children implanted before 2 years of age compared to those implanted between ages 3–5 (Dettman et al., 2016; Tobey et al., 2013); infants who received CIs within the first two years of life show increased phonetic complexity in their utterances, which correlates with language skills at 4 years of age (Walker & Bass-Ringdahl, 2008). Other studies have looked at even younger ages of implantation, and found significantly better outcomes in children implanted before 12 months of age than from 13–24 months (Colletti, Mandalà, Zoccante, Shannon, & Colletti, 2011; Cuda, Murri, Guerzoni, Fabrizi, & Mariani, 2014; Dettman et al., 2016; Dettman, Pinder, Briggs, & Dowell, 2007; Leigh, Dettman, Dowell, & Briggs, 2013).

It is important to recognize, however, that the fact that CIs are "effective" does not necessarily mean that CI users' speech production and perception are indistinguishable from their normally hearing peers: mean levels of performance decrease with age of implantation, and variability increases. For example, children implanted before 2 years of age showed an average of 12 months' delay in receptive language abilities at 2–4 years, relative to hearing children (Ceh, Bervinchak, & Francis, 2013). In another study of a group of children who received CIs prior to age 5 and were tested at ages 5–13 years, only approximately 50% were in the normative range for their age on assessments of spoken language (Boons et al., 2013). In a large national study of a cohort of children who were among the first in the United States to receive multichannel CIs, only about 50% of children were within one standard deviation of norms obtained from hearing children on tasks of receptive and expressive language, although this increased to 70%–80% in the normal range by high school (Geers, Strube, Tobey, Pisoni, & Moog, 2011). However, there was still considerable variability in individual outcomes, and the authors of this study noted significant gaps between verbal and nonverbal IQ scores in CI users, suggesting that the CI users had not reached levels of spoken language competence that they might have been able to without a hearing impairment. These studies further noted that children who evidenced greater language difficulties in early grades were also those with worse performance in high school. This suggests that although the proportion of children falling within the normal range increased with age, time alone is not a panacea; identifying and addressing the needs of CI users who are struggling early on might help improve long-term outcomes. Further, CI users' performance varied widely across different outcome measures; generally they performed worse on more challenging tests (e.g., connected speech compared to isolated words), and better on tests where strategies or executive skills (such as use of context) could compensate for hearing difficulties (Geers, Pisoni, & Brenner, 2013; Geers & Sedey, 2011).

While CIs are able to open up the world of sound to children at any age (and even adults), the data on age of implantation are consistent with the animal literature pointing to sensitive periods in auditory development (reviewed in the next section), as well as the many linguistic milestones that normally hearing infants achieve in the first year of life (see, e.g., Kuhl, 2004, for a review). The precise timing of such sensitive periods, and the extent to which language outcomes are affected by auditory versus linguistic sensitive periods, are not clear because there are very few cases in which children develop with normal hearing but no linguistic input—and those cases that do exist, such as neglected children and those in some orphanages, are confounded by much broader deficits in the children's environments, such as impoverished social and emotional interactions. Furthermore, although the outcomes of children implanted prior to 1 year of age are significantly better than those implanted later, not all of those children necessarily achieve the same language outcomes as normally hearing peers. It will be important in the future to study outcomes as a function of age of implantation among children implanted prior to 1 year—given the rapid rate of development in this period, it may well be that implantation at 6, 8, or 12 months has as-yet undocumented differences in outcomes. On the other hand, the phenomenon of suspended auditory development in animal models (see next section) suggests that a "younger is always better" approach may not necessarily hold true across the first 12 months of life. Rather, there may be a lower limit on how young a child needs to be to receive maximum benefit from a CI.

It is also important to note that—while neurobiological sensitive periods doubtless play a major role in determining CI outcomes—when children receive a CI, they are not provided with acoustic information that is as rich as normal hearing. Thus it is not simply a case of auditory deprivation followed by normal hearing. CIs have between 8–32 channels (frequency bands) that they encode. In other words, whereas the intact cochlea encodes frequency along an effectively continuous range, a CI stimulates only 8–32 locations along the cochlea, although the auditory system adapts over time in such a way that experienced CI users are able to resolve a much finer-grained range of frequencies than the few that are directly encoded by the CI electrode. Nevertheless, children receiving CIs face (at least) two challenges: the effects of auditory deprivation on neurodevelopment, and learning to extract and make sense of the information necessary to understand speech from a degraded stimulus. In the following sections we will first examine the neurodevelopmental consequences of auditory deprivation, followed by consideration of the factors—other than age at implantation—that seem to mediate language outcomes in deaf children.

NEURODEVELOPMENTAL CONSEQUENCES OF AUDITORY DEPRIVATION

In order to better understand how deafness and CIs affect language processing, it is helpful to understand the effects of acoustic deprivation on brain organization and structure. This has been extensively studied in an animal model of congenital deafness: blue-eyed white cats (Ponton & Eggermont, 2002). A large proportion of these cats are born with a mutation that causes a lack of hair cells (the acoustic receptor cells in the cochlea), which is a common cause of deafness in humans as well. Studies using these cats have allowed for a better understanding of how cells in the auditory system develop in the absence of acoustic input, and also what impact cochlear implantation at different ages has on the development and organization of the auditory system. These studies (reviewed in Kral & Sharma, 2012) have shown that in the course of normal auditory development, cells become tuned to particular acoustic features (such as frequency, or sensitivity to inter-aural timing differences) through experience. However, even in the absence of auditory input, a very rudimentary organization around these features still exists. This suggests that coarse genetic coding guides the organization of the auditory system, but that experience is critical to refine the general "outline" provided by genetics, and to properly tune cells. In addition, with experience, hearing animals (and people) develop auditory object representations, learning to associate particular sounds with particular objects in the world (including environmental noises, such as food being poured into a bowl; voices associated with individuals; and—at least in humans—speech). Thus cells' tuning during normal auditory cortex development is driven by a combination of both bottom-up (sensory) and top-down (cognitive) influences.

Since the top-down influences rely on representations of complex combinations of acoustic features, the bottom-up development necessarily starts first. This process has been shown to be subject to sensitive periods, such that normal development can occur only with acoustic exposure early in life. In cats, the sensitive period appears to be in the first 4 months of life: cats receiving CIs prior to this age show normal, or nearly normal, patterns of electrophysiological responses to sound after CI experience (measured by electrodes placed directly in A1—primary auditory cortex), whereas cats implanted later show much weaker and less organized responses—even after the same total duration of acoustic stimulation (Kral & Sharma, 2012). These changes in sensitivity seem to be caused by a combination of factors, including changes in neurotransmitter receptor density, the duration of postsynaptic potentials, dendritic branching, synaptogenesis, overall cortical inhibition, and structural changes in auditory cortex. In cases of auditory deprivation, the development of these processes is delayed for the first two months of life, and then proceeds in the absence of stimulation, albeit with much-degraded organization and sensitivity. Thus, to a certain extent, a lack of auditory stimulation seems to extend the temporal window of the sensitive period—creating a wider window for restoring hearing with minimal consequences—but this delay only lasts so long before self-organization begins to occur, even without input. A further consequence of this development that occurs in the absence of hearing is that it seems to reduce neuroplastic sensitivity to external input (Kral & Sharma, 2012).

In humans, neuroimaging offers a powerful way to study the effects of deafness and cochlear implantation on language processing, and potentially provide insights into what underlies suboptimal outcomes. Several imaging modalities have been used to study deaf people and CI users, including positron emission tomography (PET), structural magnetic resonance imaging (MRI), functional MRI (fMRI) (see Heim & Specht, Chapter 4 in this volume), functional near infrared spectroscopy (fNIRS) (see Minagawa & Cristia, Chapter 7 in this volume) and electroencephalography (EEG), including event-related potentials (ERP; EEG time-locked to stimulus events of interest) (see Leckey & Federmeier, Chapter 3 in this volume). One significant limitation imposed by cochlear implants is the fact that they are implanted electromagnetic devices containing metal. Since MRI uses strong magnetic fields and radio frequency waves, it is not possible to perform research MRI scans on people with CIs.

The developmental time course in humans is (not surprisingly) more protracted than in cats. Auditory brainstem potentials take approximately 2 years to reach adult-like shape and timing, and cortically generated auditory evoked potentials (AEPs; electrical recordings from the scalp) take longer, ranging from 2 years (for the P2 component) into adolescence (for the N1; Eggermont & Ponton, 2003). The development of these potentials reflects underlying changes in the maturation of auditory cortex, most notably myelination of axons; postmortem histological studies have shown that in most cortical layers this myelination begins between 4.5–12 months and matures between 3–5 years, though the auditory system is not fully mature until around 12 years. Studies of AEPs in CI users show results that parallel this developmental time course. A large study of people who received CIs at different ages examined the P1 component, which reflects the earliest processing of sound in the auditory cortex (Sharma, Dorman, & Kral, 2005; Sharma, Dorman, & Spahr, 2002). This study demonstrated that children who received CIs before 3.5 years of age ultimately showed P1 AEP latencies within the normal range, whereas those implanted after age 7 never showed normal P1 latencies, even after many years of use. Those implanted between 3.5–7 years showed more variable, intermediate outcomes, leading Sharma and colleagues to conclude that implantation prior to 3.5 years was optimal from a developmental neurophysioloical point of view, with a window of decreasing sensitivity up to 7 years. Eggermont and Ponton (2003) note that for early-implanted children, the delays in P1 latency quite closely track the duration of deafness; in other words, P1 latencies appear normal when adjusted for the duration that the child has received auditory stimulation. They further note that the P1 likely reflects projections from the thalamus to cortical layers III and IV, which are relatively slow to mature.

Similar results have been obtained for the N1 AEP, which occurs after the P1 and also reflects early stages of cortical auditory processing. The N1 normally begins to be detectable in the AEP at around 7 years of age, associated with maturation of cortical layer II in A1 and thalamo-cortical projections (Eggermont & Ponton, 2003). The development of this component continues up to approximately age 9–12 years, which coincides cortically with the development of A1 layers II and III, and behaviorally with improvements in speech in noise perception (Eggermont & Ponton, 2003). Sharma and colleagues (2015) examined N1 development in 80 CI users aged 2–16 years, as well as normally hearing children of similar age. The N1 began to be detectable in the AEP waveforms in both normally hearing and early-implanted (<3.5 years) CI users by 6–9 years, and was identifiable in all early implantees by 9–12 years. In contrast, among children implanted after the age of 7, the N1 was not detectable in any children under age 12, and only a small percentage of the older children; as with the P1, children implanted between 3.5–7 years showed intermediate responses, with less robust N1s than younger-implanted children. Ponton and Eggermont (2002) also examined N1 latency, in a smaller group of CI users, and found that N1 showed permanent increases in latency compared to normally hearing children. In a large study of 79 CI children with a wide range of hearing experience, Jiwani and colleagues (2013) noted that although differences in AEPs between normally hearing and CI children decreased over time, they were still present even with 10 or more years of hearing experience. Ponton and Eggermont suggested that immature myelination of layer I, arising from lack of early auditory stimulation, might result in poorly synchronized firing patterns that create a smeared and imprecise signal, affecting the N1 as well as auditory performance in noisy situations.

Structurally, congenitally deaf adults show no changes in gray matter volume in the superior temporal gyrus (STG) generally, nor in A1/Heschl's gyrus specifically (Emmorey, Allen, Bruss, Schenker, & Damasio, 2003; Leporé et al., 2010; Penhune, Cismaru, Dorsaint-Pierre, Petitto, & Zatorre, 2003; Shibata, 2007). However, reductions in white matter volume have been reported (Emmorey et al., 2003; Olulade, Koo, LaSasso, & Eden, 2014). A study of deaf infants similarly showed decreased white matter in Heschl's gyrus, as well as increased gray matter volume (Smith et al., 2011). These findings are consistent with Ponton and Eggermont's (2002) suggestion of immature myelination. Outside of the auditory cortex, several other structural differences have been reported, including increased white matter volumes in the frontal lobes, corpus callosum, and insula (J. S. Allen, Emmorey, Bruss, & Damasio, 2008; Leporé et al., 2010); also, gray matter volume is increased in the left insula (J. S. Allen et al., 2008) and left motor cortex (Penhune et al., 2003). Conflicting results have been obtained for the primary visual cortex, where one study reported increases in gray matter (J. S. Allen, Emmorey, Bruss, & Damasio, 2013), while another reported decreases (Olulade et al., 2014). While these structural changes have not been correlated with specific functional abilities, nor with CI outcomes, it can be speculated that white matter reductions in auditory cortex reflect a lack of activity-dependent strengthening of these pathways, which could in turn negatively affect CI outcomes.

While most functional neuroimaging studies have focused on task-related activity in CI users (e.g., during speech processing), one PET study examined baseline (resting, not task-related) glucose metabolism measured prior to implantation in a group of children aged 1–11, and related this to their speech processing outcomes 3 years later (H.-J. Lee et al., 2007). Auditory speech comprehension was positively correlated with metabolic activity in the left dorsolateral prefrontal cortex (associated with motor/premotor tasks and verbal working memory) and angular gyrus (associated with phonological processing). Conversely, speech comprehension was negatively correlated with metabolism in other areas, notably the right STG including Heschl's gyrus. The authors interpreted these findings as indicating that higher spontaneous neural activity in auditory/periauditory regions may reflect neuroplastic reorganization, whereby these regions assume other functions, and thus could not later assume a role in auditory processing—a topic discussed further in the next section.

A number of other studies have examined brain activation after cochlear implantation, using functional PET imaging to measure blood flow reflecting task-related activity. Studies have consistently reported auditory cortex activation by auditory stimuli (speech and non-speech) in deaf adults after cochlear implantation, and many have shown activation of classical left hemisphere language areas as well, including Broca's and Wernicke's areas (Giraud et al., 2000; Herzog et al., 1991; Ito, Iwasaki, Sakakibara, & Yonekura, 1993; Limb, Molloy, Jiradejvong, & Braun, 2010; Naito et al., 1995; Okazawa et al., 1996; Truy et al., 1995). A few studies have related brain activation to CI outcomes, and generally show higher levels of activation within auditory and language regions in people with better speech comprehension (Fujiki et al., 1999; K. M. J. Green, Julyan, Hastings, & Ramsden, 2005; Mortensen, Mirz, & Gjedde, 2006). While these findings—showing correlations between CI outcomes and brain activity markers—make intuitive sense, several caveats are important to note. First, all of these studies were based on extremely heterogeneous groups of CI users—varying in their ages of hearing loss (including a mix of pre- and post-lingually deafened people), duration of deafness, and duration of CI use. This reflects the difficulty of performing this type of research: adult CI recipients are inherently a highly heterogeneous group, and there are relatively few CI users in any given location. Of these, only a small subset is likely to be interested in undergoing in a PET scan (which involves radioactive tracers) and also to meet the inclusion criteria for the study. However, this poses significant challenges for interpreting the imaging data, especially the comparisons based on speech comprehension. In all of these studies, good and poor comprehenders differed in important variables, such as age of onset of hearing loss, duration of loss, and duration of CI use—all of which likely contributed to an individual's performance level. Moreover, most of these studies had relatively few participants overall, and fewer when these were divided into subgroups based on performance. Thus, what appears as no activation in a lower-performing group may be weaker activation combined with insufficient statistical power to detect that activation. Overall, the small sample sizes in the neuroimaging studies of CI users published to date is of real concern, especially given the growing recognition that many neuroimaging studies are underpowered (Button et al., 2013). As such we are posed with a “chicken and egg” question: Do CI users who achieve better speech perception outcomes do so because they are better able to engage particular brain areas, or do they show greater brain activation as a consequence of their better performance?

Neuroplastic Reorganization in Deafness

The fate of auditory cortices in the absence of acoustic stimulation is mixed. On the one hand—consistent with the folk adage that when one sense is lost, the others are enhanced—some parts of the auditory system show evidence of takeover by other sensory systems. Evidence for this was first provided in humans, with congenitally deaf adults outperforming normally hearing adults on a task involving motion detection in the attended, peripheral visual field (Neville & Lawson, 1987). Notably, in this study deaf adults also showed both an enhanced visual N1 ERP component to attended peripheral visual stimuli (but not centrally presented stimuli), and an altered scalp topography of the N1, whereby its peak was shifted anteriorly from occipital to temporal regions. Although the location of an electrical potential on the scalp cannot accurately inform us as to the location of its generators in the brain, Neville and Lawson speculated that this reflected takeover of auditory cortex for visual processing.

Subsequent work has replicated and extended Neville and Lawson’s (1987) original findings, and has revealed that although deaf people’s visual abilities are not enhanced across the board, they do show consistent improvements on some specific tasks. Studies have failed to find any consistent differences between deaf and hearing individuals in most visual functions, including sustained attention, visual search, orienting or alerting aspects of attention, or low-level functions such as contrast sensitivity, motion-detection thresholds, or brightness detection (Bavelier et al., 2001; Bavelier, Dye, & Hauser, 2006; Bosworth & Dobkins, 2002a; Horn, Davis, Pisoni, & Miyamoto, 2005). Rather, congenitally deaf people—both adults and children—show a very specific profile of greater sensitivity in tasks requiring selective attention to the visual periphery (Bosworth & Dobkins, 2002a; Bottari, Nava, Ley, & Pavani, 2010; Dye, Baril, & Bavelier, 2007; Dye, Hauser, & Bavelier, 2009; Neville & Lawson, 1987), and to visual motion (Bosworth & Dobkins, 1999, 2002b; Mohammed et al., 2005; Neville & Lawson, 1987; Stevens & Neville, 2006). Congenitally deaf adults and children also evidence more interference when distracting stimuli are presented in the visual periphery, but less interference from stimuli presented centrally, than normally hearing individuals (Dye et al., 2007; Dye et al., 2009). Sign language experience itself leads to a right visual field superiority for motion detection, in contrast to the left field advantage typical of hearing non-signers (Bosworth & Dobkins, 1999, 2002b; Hauthal, Sandmann, Debener, & Thorne, 2013).

Similar selective enhancements have been shown in cats, along with associated reorganization of specific auditory regions. In an elegant study by Lomber and colleagues (Lomber, Meredith, & Kral, 2010), small cooling coils were implanted in cats' brains to allow transient deactivation of specific cortical regions. When the posterior auditory field was transiently deactivated, congenitally deaf cats' enhanced peripheral visual localization abilities were reduced to levels consistent with normally hearing cats, indicating a direct causal link between deaf cats' enhanced performance and this brain area. Interestingly, in normally hearing cats this area subserves the localization of sounds, so it seems that the takeover of auditory processing regions by vision was specific to regions already involved in spatial localization. As well, deaf cats' enhanced sensitivity to visual motion was reduced to the levels of normally hearing cats by transient deactivation of a different part of auditory cortex, the dorsal zone. Although the function of this region in normally hearing cats is unknown, later work showed that in deaf cats, this area receives some direct axonal projections from visual and somatosensory cortices (Barone, Lacassagne, & Kral, 2013). At the same time, this work demonstrated no effects on visual processing when either A1 or several other auditory cortical regions were deactivated. This indicates that in the absence of auditory input, cortical auditory regions are not universally taken over for other purposes; rather, much of this cortex retains a rough approximation of its normal organization. In terms of the implications of this for CI outcomes, the animal evidence clearly suggests the existence of sensitive periods in development such that earlier implantation is likely to ultimately result in a more typical pattern of organization. Nonetheless, in the absence of early intervention, much of the auditory system appears to remain unoccupied, rather than being taken over for other sensory or cognitive functions.

The behavioral work in cats and humans, along with the neurophysiological work in cats, is also supported by some neuroimaging evidence, although the picture is less clear than in the animal model. These data are almost entirely from congenitally deaf adult sign language users who did not have CIs. In one set of studies, deaf signers (but not hearing people) showed right STG activation (including Heschl's gyrus) when viewing moving dots in the peripheral visual field (Fine, Finney, Boynton, & Dobkins, 2005; Finney, Fine, & Dobkins, 2001). However, this finding was not replicated in other studies using very similar stimuli (Bavelier et al., 2000; Bavelier et al., 2001)—which found instead changes in lateralization and functional connectivity within the same set of regions used for visual processing in hearing people. More recently, Cardin and colleagues (2013, 2016) showed primary auditory cortex activation by sign language both in deaf signers and—most notably—in deaf non-signers, but not in hearing non-signers. Another study showed that cortical thickness in right planum temporale correlated with visual motion-detection thresholds in congenitally deaf signers (Shiell, Champoux, & Zatorre, 2016). Further, in a recent study of deaf, non-signing adults with a range of ages of hearing loss, Muise-Hennessey and colleagues (2015, 2016), found that both earlier onset and longer duration of deafness were associated with stronger left STG (though not A1) activity when viewing communicative gestures; this activation was not present in normally hearing people. Collectively, these data suggest that deafness increases the sensitivity of auditory cortex to moving visual stimuli, regardless of sign language experience.

Some research has specifically investigated relationships between CI use and visual processing or visual interference. Doucet and colleagues (2006) reported that while proficient CI users showed enhanced visual N1 and P2 ERP components in response to moving visual stimuli, poor CI users showed smaller visual ERP components that, critically, were shifted anteriorly on the scalp compared to the ERPs of normally hearing or proficient CI users—similar to Neville and Lawson's (1987) early findings. Other studies have investigated more directly how visual information affects speech processing in CI users. Champoux and colleagues (2009) investigated speech processing in the presence of different types of visual distractors. Proficient CI users performed comparably to normally hearing adults; however, CI users with poorer auditory-only speech comprehension showed greater interference during speech processing in the presence of moving visual stimuli (but not color-change distractors). Other studies investigated how the auditory perception of phonemes is influenced by whether the listener sees the same or a different phoneme being mouthed (Desai, Stickney, & Zeng, 2008; Rouger, Fraysse, Deguine, & Barone, 2008; Tremblay, Champoux, Lepore, & Théoret, 2010). CI users showed greater influence of visual information on their speech perception overall, and those with poorer speech perception showed relatively greater reliance on visual information (Tremblay et al., 2010). However, reliance on visual information during normal speech processing does not appear to impede auditory processing. A longitudinal study found that CI users who showed significant gains in auditory-only processing after receiving a CI maintained high levels of speechreading (sometimes referred to as lipreading) ability; the authors suggested that this was due to the fact that CI users have greater difficulty perceiving auditory speech in noisy environments, and so continue to rely on visual cues to aid speech perception, even when the CI is effective (Rouger et al., 2007).

Given the evidence suggesting cross-modal reorganization in deaf people, an important question is whether enhanced sensitivity of auditory cortex to visual information interferes with hearing after cochlear implantation. One possibility is that if areas normally specialized for auditory processing do take on other functions, then restoration of hearing through a CI might be less effective if these areas are forced to reorganize themselves, or are even unable to assume auditory processing functions once years of activity-dependent neural connections have been established. On the other hand, Campbell and MacSweeney (2014) have noted that even normally hearing people show activation within auditory regions of the STG for some types of stimuli, such as speechreading (Calvert & Campbell, 2003) and sign language (in hearing native signers; Neville et al., 1998). Further, Rouger and colleagues' (2007) data suggest beneficial effects of at least one specific enhanced visual ability (speechreading) on speech perception, even after a CI. Thus if there is visual "takeover" in deafness of brain areas typically used for auditory processing, it appears to be more nuanced than an area being simply unimodally "auditory" in normally hearing people, and "visual" in deaf people. Although studies have shown visual interference and altered ERP topography in CI users with poor speech comprehension, the directionality of these effects is not clear. One interpretation is that visual takeover of auditory cortex mediates these effects, leading to poorer CI performance. However, there are many factors that contribute to CI outcomes, as discussed previously and in the following two sections. Therefore it is possible that visual activation of auditory cortex does not interfere with speech processing, but rather represents a compensatory mechanism whereby people who are unable to obtain optimal auditory information continue to rely to a greater extent on visual information. As a result, they show overall greater sensitivity to such information—which can manifest in some circumstances as visual interference. However, outside of experimental lab settings, visual information is usually beneficial to speech comprehension rather than detrimental, and so evidence of such interference should not necessarily be interpreted as a negative phenomenon.

Factors Influencing CI Outcomes in Children

As we have seen, age at implantation is a very strong predictor of CI outcomes, with implantation within the first year of life yielding the best outcomes in congenitally deaf children. Related to this, in children not born deaf, earlier onset and longer duration of deafness both predict worse outcomes (Geers, 2003; Sarant et al., 2001). However, this does not explain all the variance in CI outcomes; a number of other factors have been identified consistently across multiple studies that influence CI outcomes.

The home and family setting in which a child is raised has very strong influences on the linguistic and educational achievements of all children (Hart & Risley, 1995; 2003; Hoff-Ginsberg, 1998), and children with CIs are no different. Socioeconomic status (SES) is a significant predictor of language outcomes in children with CIs (Convertino, Marschark, Sapere, Sarchet, & Zupan, 2009; Geers, 2003; Hodges, Ash, Balkany, Schloffman, & Butts, 1999; Niparko, Tobey, Thal, & Eisenberg, 2010), as is maternal education status (which is closely related to SES; Sarant, Harris, Bennet, & Bant, 2014)—higher SES and maternal education levels predict better outcomes. Parental behavior also impacts outcomes in several ways. Mothers who speak in longer, more complex sentences to their children (mean length of utterance—MLU) have children with better language outcomes (DesJardin & Eisenberg, 2007), whereas the children of mothers who use more directives and prohibitions have poorer language outcomes (Fagan, Bergeson, & Morris, 2014). Maternal sensitivity, the level of parental involvement, and cognitive stimulation provided to children also influence outcomes (Moeller, 2000; Quittner et al., 2013; Sarant, Holt, Dowell, Rickards, & Blamey, 2008).

Parental sensitivity can be a double-edged sword, however: data suggest that many mothers adapt their speech to their expectations of deaf children's limitations in understanding speech—producing simpler utterances on the expectation that this will be easier for the children to understand—which reduces the complexity of language input and may adversely affect language development (Fagan et al., 2014). It seems likely that the effects of SES and maternal education on outcomes are at least in part mediated by these parenting style variables, since better-educated mothers tend to provide their children with richer input (Hart & Risley, 1995, 2003). However, studies have also shown that positive interaction behaviors can be taught, and indeed intervention programs that teach parents positive interaction styles with their deaf children significantly improve the children's CI outcomes (Moog & Geers, 2010). Related to this, having a deaf family member improves CI users' outcomes, likely due to a combination of increased sensitivity to the specific needs of deaf children, and more sign language knowledge and use (Hassanzadeh, 2012; Sarant et al., 2014). Beyond SES and parenting effects, children born earlier than their siblings (birth order) and/or having fewer siblings show better outcomes (Geers, Brenner, & Davidson, 2003; Sarant et al., 2014), and girls often do better than boys (Geers, 2003; Sarant et al., 2014).

Cognitive factors also significantly influence CI outcomes. Among these, the ones that have been most consistently identified as strong predictors are nonverbal IQ (Geers, 2003; Geers et al., 2003; Pyman, Blamey, Lacy, Clark, & Dowell, 2000; Sarant et al., 2014; Sarant et al., 2008) and aspects of working memory—including working memory capacity, and the speed and efficiency of rehearsal and retrieval (Geers & Sedey, 2011). Motor skills are also closely related to CI outcomes: children with a history of fine motor problems have poorer outcomes (Pyman et al., 2000; Sarant et al., 2014), as do those with slower trajectories of motor development (Horn, Fagan, Dillon, Pisoni, & Miyamoto, 2007; Horn, Pisoni, Sanders, & Miyamoto, 2005).

Genetics may also influence outcomes. This has been studied primarily in the context of mutations to the connexin-26 (GJB2) gene—a leading cause of congenital deafness in many countries (Denoyelle et al., 1997; G. E. Green et al., 2002). The data are equivocal, however, with some studies reporting better outcomes for children with GJB2 mutations than with other causes of deafness (C.-M. Wu et al., 2015), but others reporting no differences (C.-C. Wu, Lee, Chen, & Hsu, 2008). Another mutation, to the SLC26A4 gene, has been associated with more positive outcomes (C.-M. Wu et al., 2015); this study further found that GJB2 and SLC26A4 mutations positively affected outcomes only in children implanted prior to age 3, but not in children implanted later.

Finally, whether cochlear implantation is unilateral or bilateral may influence outcomes. Bilateral implants were initially proposed because with normal hearing, sounds are localized using timing and phase difference cues from the two ears. Not only does localizing the origins of sounds help in orienting to the environment (which can help both identify where a speaker is, and where a danger such as oncoming traffic may be coming from), but it may help speech perception in noisy environments as well, by helping to focus auditory attention. Indeed, children with bilateral implants outperform those with unilateral implants—and also do better with both implants activated than only one—both on sound localization (Beijen, Snik, & Mylanus, 2007; Galvin, Mok, & Dowell, 2007; Litovsky, Johnstone, Godar, & Agrawal, 2006; Lovett, Kitterick, Hewitt, & Summerfield, 2010) and speech in noise perception (Beijen et al., 2007;

Lovett et al., 2010; Peters, Litovsky, Parkinson, & Lake, 2007; Wolfe, Baker, Caraway, & Kasulis, 2007; Zeitler, Kessler, & Terushkin, 2008). These results also translate into better use of auditory and vocal skills in social interactions (Tait et al., 2010), and better performance on standardized language tests (Sarant et al., 2001).

Although virtually all studies comparing bilateral with unilateral implantation have reported bilateral advantages, there are some caveats to this. First, not all measures used show bilateral advantages, including subjective assessments of speech and quality of hearing (Beijen et al., 2007) and preschool language scales (Sarant et al., 2001). Second, the timing of the implants plays an important role in outcomes. Bilateral implantation is rarely simultaneous; it typically occurs sequentially, with the second implant being received months or even years after the first. The data indicate that the closer together the two CIs can be implanted, the better the outcomes are (Sharma et al., 2005). With longer separations between the first and second implants, children have more difficulty both adjusting to the second implant, and in integrating auditory input from the two sources. Related to this, speech in noise perception and localization are often significantly better when the noise occurs on the side of the first implant, and more generally hearing assessments show better performance for the first-implanted ear, especially with longer durations between the first and second implants (Galvin et al., 2007; Peters et al., 2007).

Finally, in considering the influence of so many variables on CI outcomes, it is important to consider that no research in this area has used randomized, double-blind studies that are the gold standard in clinical research (Vlastarakos et al., 2010). Rather, studies of CIs and the effects of deafness more generally reflect the results of "natural experiments" that occur as a result of the choices made by individual parents based on the options made available to them in a particular location at a particular point in time. For instance, a child born deaf in the past year in a major urban center of a developed country is very likely to be identified as deaf within days—if not hours—of being born and may well have an active CI before his or her first birthday. In contrast, this author has met people from low socioeconomic status (SES), rural communities who were identified as deaf only upon entering school and whose parents were informed by their family physician that there were no treatment options—and who thus only obtained a CI in adulthood. While this range of experiences creates a natural degree of heterogeneity that can be analyzed in an attempt to determine the influence of certain variables, the end result is that the variables are confounded and often difficult to disentangle.

Conclusions

The first and clearest take-home message from this chapter is that cochlear implantation is highly effective in restoring hearing, and earlier implantation (certainly before 3.5 years, and probably optimally before 1 year) leads to better outcomes than later implantation. Nevertheless, CIs are not magical spells that fix all the effects of hearing loss: children with CIs need specific supports in their language development, including parenting styles and in many cases additional supports in school, especially in early grades.

Even when CIs are readily available (which is not the case in many places for reasons such as cost and access to services), there will inevitably be a waiting period prior to the CI surgery, and an additional period is required post-surgery before the CI is activated and the child begins receiving auditory input—followed by additional time adapting to the CI before speech is perceived at all clearly. Although hearing aids may be provided during the interval before CI activation, for children whose hearing loss is so profound as to warrant a CI, these will provide little support for language development. The period between diagnosis and a level of restored hearing capable of supporting speech comprehension is thus likely to be months or even years. It is clear that parents should not simply wait for a CI before their children begin to receive language input—the first year of life is filled with critical/sensitive periods for language development that rely on language input. Sign language is the only natural human language that deaf children are able to perceive, and the evidence suggests that this should be provided, as much as possible and as early as possible—even if it is expected that children will rely primarily or exclusively on spoken language after their implant.

There is room in the middle ground for hearing parents to provide the optimal linguistic environment for their infant prior to cochlear implantation. Although parents who are new to signing cannot provide fluent, native-like input, there is strong evidence that young children pick up on linguistic structure and regularities even in imperfect, inconsistent input from nonfluent parents, and end up producing more linguistically regular output (Brentari, Coppola, Mazzoni, & Goldin-Meadow, 2011)—a testament to the readiness of infant brains to learn from language input. Parents do not need to become fluent signers in order to provide their deaf children with constructive language input—indeed, in recent years many parents of children with normal hearing have taken it upon themselves to learn “baby sign” (ASL vocabulary) to facilitate communication and bonding with their infants. This practice is supported by empirical evidence pointing to positive language development and stronger parent-child interactions, suggesting that there is benefit—and critically, no cost—to exposing children to sign language (Goodwyn, Acredolo, & Brown, 2000; Kirk, Howlett, Pine, & Fletcher, 2012; Mueller, Sepulveda, & Rodriguez, 2013). Put another way, there is no evidence that depriving children of natural language input leads to better language outcomes than providing them with imperfect input.

Providing deaf infants with sign language input prior to their receiving a CI—and even continuing afterward in some settings—should simply be viewed as a form of bilingualism. A vast proportion of children in the world are raised in multilingual households, without negative consequences to their development (and possibly even benefits; see, in this volume, Green & Kroll, Chapter 11, and Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24). For parents who worry that their child’s deafness is a disability and that bilingualism will be an additional burden, we can point to the data showing that children exposed to sign language from birth show normal language development, regardless of whether they are deaf and learn only sign language as an L1

(Mayberry et al., 2002), or whether they are hearing, native sign-speech bilinguals (K. Davidson et al., 2014). In this context, it is also worth noting that even children with severe intellectual disabilities such as Down's syndrome and autism spectrum disorder do not show any costs to being raised bilingually (e.g., English-French) as opposed to monolingually (Bird et al., 2005; Ohashi et al., 2012). Beyond the irreplaceable benefits of natural language input during the critical first year of life, providing children with sign language prepares them for participation in Deaf culture. Although many deaf children may be raised in hearing families, educated in mainstream classrooms, and rarely or never encounter other deaf children, they may ultimately find important support and identity within Deaf culture—even if they achieve excellent hearing outcomes with a CI.

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PART III

ARTICULATION AND PRODUCTION

CHAPTER 15

NEUROMOTOR ORGANIZATION OF SPEECH PRODUCTION

PASCALE TREMBLAY, ISABELLE DESCHAMPS,
AND ANTHONY STEVEN DICK

Introduction

The act of speaking is a complex and integrative behavior, which associates high-level cognitive and linguistic processes with fine motor-control mechanisms. Speaking begins with an intention to communicate, continues to the translation of the message into lexical units (words), which in turn need to be broken down into sequences of temporally ordered syllables and adjusted to the context in terms of rhythm, loudness, and prosody. The final stage requires the coordination of multiple sensorimotor systems, including the respiratory system, which provides the airflow necessary to set the vocal folds into vibrations, the intrinsic and extrinsic laryngeal muscles that convert this airflow into phonation, and, finally, the supralaryngeal muscles that modulate the configuration of the vocal tract to convert the laryngeal output into vowels and consonants (articulation). Speaking also requires the interaction of sensorimotor mechanisms with linguistic processes including grammatical, syntactic, and semantic processes, as well as cognitive/executive processes such as verbal memory and audiovisual attention. In spite of this remarkable complexity, adult speakers are able to produce as many as six to nine syllables per second (Kent, 2000). Perhaps given this extraordinary speed and complexity, the manner in which this process is accomplished at the neural level has not been fully elucidated. Historical models of spoken language production have focused on a single region for speech production ("Broca's area") and a single region for comprehension ("Wernicke's area"), and a single white matter pathway connecting these regions (the arcuate fasciculus). The complexity of the sensorimotor processes supporting articulation has thus been minimized, and is often represented as a "final-output stage" black box within serial and compartmentalized models of language (for a discussion of this topic, see Tremblay & Dick, 2016). More recently, advances in brain imaging and brain stimulation techniques have contributed tremendously to uncovering the sophisticated neural system that underlies the production of speech. The seminal meta-analysis conducted by Indefrey and Levelt (2004) was among the first to highlight the complexity of the cortical network underlying word production. More recent analyses of functional connectivity support the notion of a highly distributed network (Simonyan, Ackermann, Chang, & Greenlee, 2016; Simonyan & Fuertinger, 2015). Here we propose, in Figure 15.1, an overview of the cortico-subcortical network that underlies speech production from phonological planning to articulation. In this chapter, we review and discuss the most up-to-date knowledge on speech production, from phonological planning to motor execution, with an emphasis on functional neuroanatomy and anatomical connectivity.

Phonological Planning for Speech Production

Phonological planning refers to the specification of the abstract phonological representations that are used during speech production. It is preceded by conceptual, lexical, semantic, and syntactic processes, and followed by motor planning, thereby representing an interface between the cognitive and the motor dimensions of speech production. The mechanisms underlying phonological planning have been studied intensively (Cholin, Levelt, & Schiller, 2006; Costa & Caramazza, 2002; Damian & Dumay, 2007; Dell & Reich, 1981; Jescheniak, Schriefers, Garrett, & Friederici, 2002; Meyer, 1990, 1991; Roelofs, 1999; Schiller, Bles, & Jansma, 2003; Schnur, Costa, & Caramazza, 2006; Shattuck-Hufnagel & Klatt, 1979; Treiman, 1985; Wheeldon & Lahiri, 1997). According to several prominent models, the phoneme and the syllable are the basic phonological units necessary to produce fluent speech (Bohland, Bullock, & Guenther, 2010; Dell, 1986; Indefrey & Levelt, 2004; Levelt, 1992, 1999; Levelt & Wheeldon, 1994; MacNeilage, 1998; Roelofs, 1997; Tourville & Guenther, 2010). During phonological planning, phonological encoding processes are called upon to build a word's phonemic and syllabic codes from abstract linguistic representations containing conceptual, semantic, and syntactic information.

Most models of speech production assume that phonological planning involves the serial retrieval of phonemic- and syllabic-level information for items that are to be produced (e.g., Bohland et al., 2010; Hickok, 2014; Indefrey & Levelt, 2004; Van der Merwe, 2009). Indefrey and Levelt (2004) propose that the phonological word forms are built online through a segment-by-segment internal syllabification process, a process associated with the left inferior frontal gyrus (IFG). According to the GODIVA

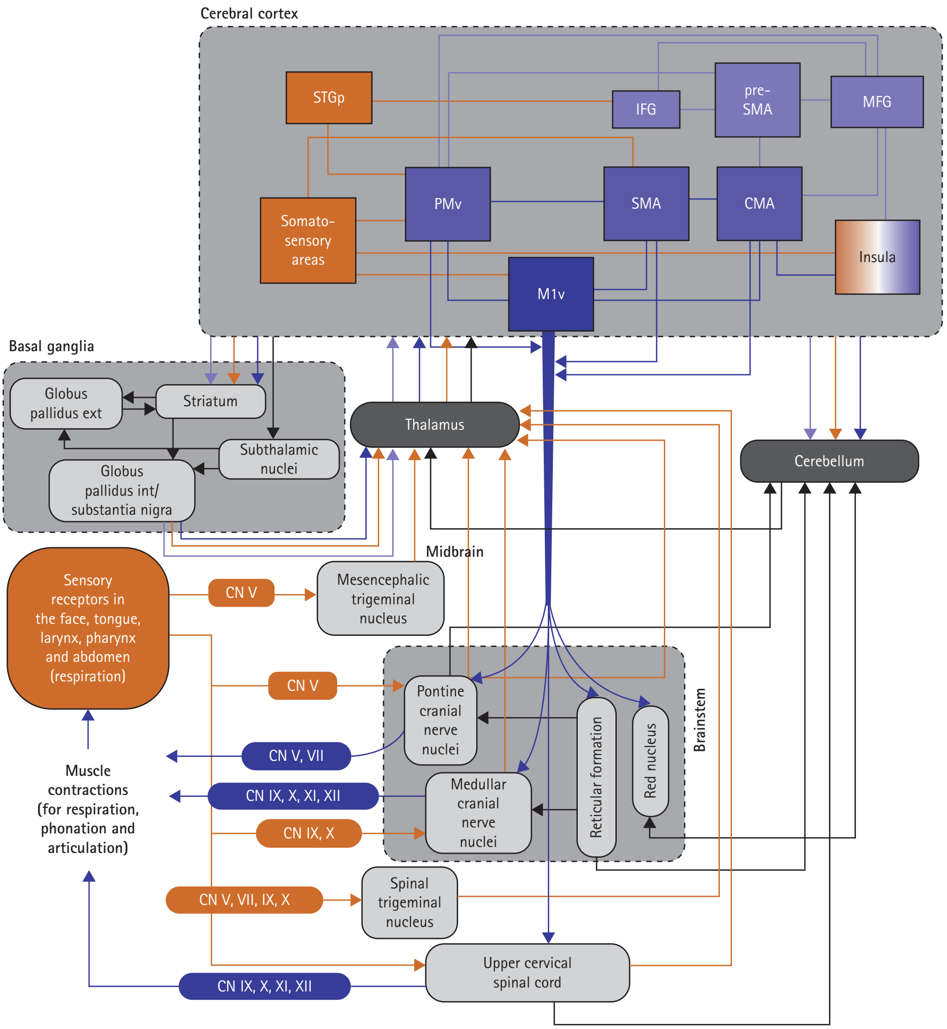
Cerebral cortex
STGp
IFG
pre-SMA
MFG
Somato-sensory areas
PMv
SMA
CMA
Insula
M1v
Basal ganglia
Globus pallidus ext
Striatum
Subthalamic nuclei
Globus pallidus int/ substantia nigra
Thalamus
Cerebellum
Midbrain
Sensory receptors in the face, tongue, larynx, pharynx and abdomen (respiration)
CN V
Mesencephalic trigeminal nucleus
CN V
Pontine cranial nerve nuclei
Reticular formation
Red nucleus
Brainstem
CN V, VII
CN IX, X, XI, XII
Medullar cranial nerve nuclei
CN IX, X
Muscle contractions (for respiration, phonation and articulation)
CN V, VII, IX, X
Spinal trigeminal nucleus
Upper cervical spinal cord
CN IX, X, XI, XII

FIGURE 15.1. Schematic representation of the neurocognitive organization of speech production. Blue lines denote connections predominantly conveying motor information. Orange lines denote connections predominantly conveying sensory information. Purple denotes connections predominantly conveying cognitive/linguistic (higher-order) information. For simplicity, the thalamus, cerebellum, and striatum were not subdivided into their subcomponents, and connections between specific cortical areas and these structures are also not included. Lines with arrows indicate the direction of the information flow. Lines without arrows indicate bidirectional connections.

Abbreviations: Globus pallidus ext: external globus pallidus; Globus pallidus int: internal globus pallidus; STGp: posterior superior temporal gyrus; PMv: ventral premotor cortex; CN: cranial nerve; IFG: inferior frontal gyrus; SMA: supplementary motor area; CMA: cingulate motor area; MFG: middle frontal gyrus.

model (gradient order DIVA) (Bohland et al., 2010)—an extension of the well-known DIVA ((Directions Into Velocities of Articulators)) model—phonemic codes and syllabic position specification are computed within the left inferior frontal sulcus, whereas syllabic frame specifications (i.e., abstract structure above the phonemic level) are associated with the pre-supplementary motor area (Bohland et al., 2010; Guenther, 1995, 2006; Guenther, Ghosh, & Tourville, 2006b; Tourville & Guenther, 2011). The notion that phonological planning is accomplished in a two-step fashion (operating serially or in parallel, depending on the speech production model) is supported by a few functional neuroimaging studies that have focused either on specific phonological representations or on the mechanisms involved in building a word's phonological form. For instance, in a recent functional magnetic resonance imaging (fMRI) experiment, Markiewicz and Bohland (2016) investigated, using multi-voxel pattern analysis (MVPA), whether the response patterns (i.e., hemodynamic response) of specific cortical areas predicted the linguistic class (i.e., phonemes and syllables) of the stimuli during the production of Consonant-Vowel-Consonant (CVC) syllables. The authors identified numerous regions spanning across both the left and right hemispheres in which predictive phoneme and\or syllable information was found. Of particular interest is the finding that the left inferior frontal sulcus was among the regions whose activation pattern was predictive of phoneme level information, consistent with GODIVA (Bohland et al., 2010). Syllable-level predictive information was found in numerous regions, including the left ventral premotor cortex (PMv) and motor cortex, as well as the left posterior superior temporal gyrus (STGp), and the right posterior superior temporal sulcus. Similarly, Peeva and colleagues (2010), using an fMRI repetition-suppression paradigm (Grill-Spector, Henson, & Martin, 2006; Grill-Spector & Malach, 2001), also identified the left PMv as a region that responds to syllabic complexity during speech-production, suggesting a role for this region in the encoding of entire syllables, perhaps through speech sound maps that represent syllabic motor programs, as proposed in the DIVA model (Guenther, Ghosh, & Tourville, 2006a). The authors also identified regions that specifically responded to phonemic complexity (the left supplementary motor area, the left globus pallidus, the left posterior superior temporal gyrus, and the left superior posterior lateral cerebellum).

Other functional neuroimaging studies have manipulated psycholinguistic variables during speech production (i.e., picture naming, reading, and spoken word/pseudo-word repetition) to target phonological encoding mechanisms, including phonological neighborhood density, and syllable and word frequency (Acheson, Hamidi, Binder, & Postle, 2011; de Zubicaray, McMahon, Eastburn, & Wilson 2002; Indefrey & Levelt, 2000; Papoutsi et al., 2009; Peramunage, Blumstein, Myers, Goldrick, & Baese-Ber, 2011; Vihla, Laine, Matti, & Salmelin, 2006). These studies have found that one region—the posterior superior temporal cortex (including the posterior segment of both the superior and middle temporal gyri)—is sensitive to these manipulations, suggesting a role for this region in phonological planning (i.e., mechanisms involved in encoding a word's phonological form).

In sum, neuroimaging experiments suggest that both the syllable and the phoneme are used during phonological planning for speech production. While many issues remain regarding the networks involved with the implementation of syllabic- and phonemic-level processes during phonological planning in speech production, empirical evidence suggests that regions distributed across the frontal and temporal lobes are involved in phonological planning. Recent promising developments of neurocomputational models of speech production (e.g., Bohland et al., 2010; Hickok, 2012) will allow researchers to test specific predictions regarding the implementation of phonological planning mechanisms.

Motor Planning/Programming for Speech Production

Speech motor planning builds upon phonological planning and possibly proceeds simultaneously. There is general agreement that the output of phonological encoding is a phonological word, in which metrical, syllabic, and segmental properties are specified. However, models of speech production differ in terms of the output of phonological planning, with some positing that the phonological form is pre-syllabified, and others postulating that syllabification occurs within the sensorimotor system. In either case, motor preparation for speech involves several steps, including response selection, motor timing, and sequencing processes. This speech motor preparation process, often globally referred to as "supra-motor" or "motor cognition" (Freund, Jeannerod, Hallett, & Leiguarda, 2005), may not be speech specific and may have evolved from more general motor functions. Thus, the system "[. . .] gets what service it can out of organs and functions, nervous and muscular, that have come into being and are maintained for very different ends than its own" (Sapir, 1921, p. 8). Several steps in this motor-planning process are specified in specific neural systems, which are reviewed in the following paragraphs. There is a growing consensus in the field of speech motor control that speech motor programs for well-practiced sounds are stored within the left PMv, as proposed in the DIVA model (Guenther, 2006). Consistent with this idea, it was recently shown, using fMRI, that the process of learning new speech sequences is associated with a decline in activation in the left PMv, suggesting that individual motor programs become merged into one, thus requiring the activation of only one motor program (Segawa, Tourville, Beal, & Guenther, 2015). Similarly, a recent electrocorticographic study conducted in awake patients showed that tissue adjacent to the PMv in the left IFG is active early on during auditory repetition, possibly reflecting the activation of speech motor plans (Flinker et al., 2015). It was found that activity was stronger for pseudo-words, which are not associated with motor programs, in contrast to real words. The contribution of the PMv and IFG to speech production has been notoriously difficult to untangle. In the Flinker study, activity in the precentral sulcus containing the PMv was not reported, leaving the question unanswered.

Motor Response Selection

The neural mechanism by which a phonological form is transformed into stored motor routines is often referred to as *response selection*, or sometimes, *action selection*. Though it is still not included in most neurobiological models of spoken-language production, motor response selection is a well-documented mechanism in the non-speech motor-control literature. Several neuroimaging studies have examined the process of selecting non-speech motor responses, including finger and hand movements. These studies have shown activation in the pre-supplementary motor area (pre-SMA) (Brodmann's medial area 6) that varied as a function of response selection modality (voluntary selection vs. forced selection) (Deiber, Ibanez, Sadato, & Hallett, 1996; Lau, Rogers, & Passingham, 2006; Weeks, Honda, Catalan, & Hallett, 2001). The pre-SMA is a region located in the medial aspect of the superior frontal gyrus, immediately anterior to the SMA and corresponding to the anterior part of Brodmann's medial area 6. The pre-SMA is densely connected to the prefrontal cortex, particularly the dorsolateral prefrontal cortex in the middle frontal gyrus (MFG) (Lu, Preston, & Strick, 1994; Luppino, Matelli, Camarda, & Rizzolatti, 1993), and to several non-primary motor areas, such as the SMA-proper and the PMv (Luppino & Rizzolatti, 2000), for controlling motor output. Recent data suggest that the pre-SMA is also connected to the posterior part of the inferior frontal gyrus through the frontal aslant tract (FAT) (Catani et al., 2012a; Ford, McGregor, Case, Crosson, White, 2010, & Dick et al., 2018). Thus, the pre-SMA has a connectivity pattern that is ideal for linking higher-level cognitive functions (including linguistic processes) and motor processes, which is critical to implementing response selection. In agreement with the literature on motor cognition, a number of fMRI studies have shown that manipulating response selection during word production modulates the pre-SMA, the neighboring cingulate motor area (CMA), and the PMv (Alario, Chainay, Lehericy, & Cohen, 2006; Crosson et al., 2001; Tremblay & Gracco, 2006; Tremblay & Small, 2011). This was also found during the selection of non-speech orofacial movements (Braun, Guillemin, Hosey, & Varga, 2001; Tremblay & Gracco, 2010). There is also evidence from neurostimulation studies that noninvasive transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume) to the pre-SMA impairs the voluntary selection of words and non-speech orofacial movements (Tremblay & Gracco, 2009). Taken together, these results suggest that the pre-SMA plays a central role in selecting motor responses for speech production and, more generally, for all voluntary actions.

In addition to a key role for the pre-SMA in response selection, recent fMRI evidence suggests a role for the striatum, and more specifically the caudate nucleus, in response selection during speech production (Argyropoulos, Tremblay, & Small, 2013). Consistent with this observation, it has been suggested that the caudate is involved in speech planning, and more specifically sequencing speech motor responses, receiving input from both the inferior frontal sulcus and the pre-SMA (Bohland et al., 2010). The caudate also has been found to be activated in memory-driven manual sequencing tasks (Menon, Anagnoson, Glover, & Pfefferbaum, 2000), and during sequence learning (Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004), which suggests the region has a role in higher- order cognitive/ executive aspects of movement preparation role in higher-order cognitive/executive aspects of movement preparation. The caudate has a connectivity pattern consistent with a role in motor planning rather than execution, as it is connected to prefrontal structures and not to the primary motor area (Alexander, DeLong, & Strick, 1986; Hoover & Strick, 1999; Postuma & Dagher, 2006).

Speech Motor Sequencing

One of the most distinctive features of spoken-language production is its serial ordering, that is, the organization of speech movements into precise, smooth, and coordinated temporal sequences of movements of the lips, tongue, and jaw (Lashley, 1951). Indeed, normal communicative speech consists of a continuous, connected stream of sounds. Motor sequencing is the planning of the specific sequences of movements required to produce smooth and co-articulated temporal sequences of movements of the lips, tongue, and jaw. Sequencing mechanisms are closely related to motor-timing mechanisms (see earlier discussion), which involve initiating movement sequences and timing each movement within a sequence. The production of streams of speech sounds thus requires the close coordination of sequencing and timing mechanisms. Neuroimaging and neuromodulation evidence shows that, for manual movements, motor sequencing is implemented in a complex and distributed neural network involving cortical premotor areas (SMA-proper, PMv), the cerebellum, and the striatum (caudate and putamen) (Bengtsson, Ehrsson, Forssberg, & Ullen, 2005; Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Macar et al., 2002); for example, repetitive TMS of the SMA-proper results in sequential timing disruptions in a complex finger-movement task (Gerloff et al., 1997). SMA-proper activation also occurs in tasks requiring the processing of temporal patterns (Macar et al., 2002). Consistent with the idea of a role for the striatum and other basal ganglia structures in motor sequencing, it has been shown that patients with basal ganglia disorders, such as Parkinson's disease (PD), a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra, have difficulty with switching rapidly from one movement to another, reflecting a deficit in the initiation and termination of sequential movements (e.g., Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992; Benecke, Rothwell, Dick, Day, & Marsden, 1987). It is also suspected that FOXP2, the transcription factor associated with impairments in articulation (Fisher & Scharff, 2009; Vargha-Khadem, Gadian, Copp, & Mishkin, 2005), affects these cortico-basal ganglia circuits (Reimers-Kipping, Hevers, Pääbo, & Enard, 2011).

For speech sequencing more specifically, a broad network appears to be involved in the process of producing sequential speech (Bohland & Guenther, 2006; Shuster & Lemieux, 2005). For example, using fMRI, Bohland and Guenther (2006) showed that several cortical regions, including the PMv, the inferior parietal lobule (IPL), the inferior frontal sulcus, the SMA, and the pre-SMA, are sensitive to serial complexity in speech-sequence production. Peeva et al. (2010) further demonstrated a contribution of the right superior lateral cerebellum to syllable sequencing.

Other studies have shown that the anterior insula, which is functionally connected to the striatum (Postuma & Dagher, 2006), is also involved in motor timing/sequencing during finger-tapping tasks (Bengtsson, Ehrsson, Forssberg, & Ullen, 2004; Lewis & Miall, 2002). Consistent with these findings, Dronkers and colleagues (Dronkers, 1996; Ogar et al., 2006) have shown, using voxel-based morphometry, that lesions to the anterior insula are related to speech apraxia, a disorder of speech planning that affects speech sequencing. Though it is unlikely that the anterior insula is involved in either speech-specific or motor-specific processes, it is a region that is active during demanding speech tasks (e.g., Ackermann & Riecker, 2004; Bilodeau-Mercure, Lortie, Sato, Guitton, & Tremblay, 2015; Bohland & Guenther, 2006; Peeva et al., 2010). It has been suggested that the anterior insula contributes to the attention-orientation system (Corbetta, Patel, & Shulman, 2008), as well as to general executive processes involved during goal-oriented tasks (Nelson et al., 2010). It is therefore possible that the insula provides the attentional control necessary to produce precisely ordered and timed sequences, which is cognitively demanding.

In sum, while there remain several questions regarding the implementation of selection and sequencing mechanisms for speech, the available empirical evidence, though limited, suggests that sequencing for speech production relies largely upon common action-control mechanisms involving the pre-SMA, SMA, PMv, insula, cerebellum, and striatum.

Speech Motor Timing

Motor timing refers to the ability to initiate movement sequences and to time each sub-movement within a sequence. It occurs at the interface of sequencing mechanisms and motor execution. For speech, initiation corresponds to the moment at which air is expelled from the lungs; it is followed by phonation, articulation, and resonance (opening or closing of the nasal cavity by the soft palate to produce nasal and oral sounds, respectively). Several regions appear to participate in motor timing, including the SMA-proper, the pre-SMA, the basal ganglia, and the prefrontal cortex. Unfortunately, though, there is little neuroimaging data focusing specifically on the neural basis of speech motor timing. An important distinction for both the neural control systems and for assessing speech motor disorders is the manner in which movements are initiated, whether externally by sensory events, or by internal events. Motor responses initiated by external stimuli are associated with activity in the SMA-proper (Lee, Chang, & Roh, 1999; Thickbroom et al., 2000; Wiese et al., 2004), as well as in the left dorsal PM (PMd) (Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Lepage et al., 1999; Weeks et al., 2001). In humans, inhibition of the left PMd results in a response delay in an externally triggered choice reaction-time task, which suggests a role in the initiation of movements (Schluter, Rushworth, Passingham, & Mills, 1998). The direct comparison of self-initiated and externally triggered finger movements reveals activation in the pre-SMA (Deiber, Ibanez, Sadato, & Hallett, 1996; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Tsujimoto, Ogawa, Tsukada, Kakiuchi, & Sasaki, 1998), which suggests that the pre-SMA may be generating internal triggers to produce actions. Using both fMRI and electroencephalography (EEG), it has been shown that the pre-SMA/SMA-proper is involved in preparing sequences of finger movements with high demands on ordering (sequencing), while the dorsolateral prefrontal cortex is involved in preparing sequences with high demands on temporal precision and timing, suggesting distinct roles for these regions in movement preparation (Bortoletto & Cunnington, 2010). Comparing self-initiated sequences to sequences in which the internal order of the sub-movements was varied also points to a role for the dorsolateral prefrontal cortex in initiation and the SMA for sub-movement timing (Bortoletto, Cook, & Cunnington, 2011). These findings are supported by TMS evidence suggesting a role for the right dorsolateral prefrontal cortex in temporal preparation for finger movements (Vallesi, Shallice, & Walsh, 2007). The right dorsolateral prefrontal cortex in the middle frontal gyrus is also thought to be part of the speech preparation network (Brendel et al., 2010; Garnier et al., 2013; Riecker et al., 2005). Consistent with evidence from finger sequence paradigms, fMRI research on speech motor preparation, though limited, suggests that several regions are involved, including the pre-SMA and SMA-proper, the bilateral putamen, the bilateral thalamus, the bilateral anterior insula, and the right dorsolateral prefrontal cortex (Brendel et al., 2010). In a recent study by Long and colleagues (Long et al., 2016), a promising cortical cooling approach was used to study speech production in awake participants awaiting brain surgery. The results show that cooling of the left IFG leads to slower speech, while cooling of the primary motor cortex (M1v) leads to articulation errors. Based on these results, the authors suggested a role for the left IFG in the control of speech timing. A role for the left IFG in the planning of speech more generally was also suggested by recent electrocorticographic recordings, which demonstrated early activity in this region during an auditory word-repetition task, which was followed by activity in M1v (Flinker et al., 2015).

There is also converging clinical and imaging data for a role for the basal ganglia in motor timing, particularly movement initiation. In patients with Parkinson's disease, there is a decline in the ability to initiate movements at will. However, externally triggered actions are preserved (Cunnington, Iansek, & Bradshaw, 1999; Freeman, Cody, & Schady, 1993; Praamstra, Stegeman, Cools, Meyer, & Horstink, 1998), which suggests a role in movement initiation for the basal ganglia, directly or through its connections with prefrontal and premotor areas. This notion is supported by fMRI studies comparing self-initiated to externally paced finger-movement sequences, which show activity in the left anterior putamen for self-initiated, but not externally paced, movements (Boecker, Jankowski, Ditter, & Scheef, 2008). For speech, Brendel et al. (2010) have shown activation of the bilateral anterior putamen during speech preparation. There is also evidence that basal ganglia dysfunction (including Parkinson and Huntington diseases) is associated with abnormal speech movement timing, including impaired movement duration (Ludlow, Connor, & Bassich, 1987), rate (Skodda, 2011; Skodda & Schlegel, 2008;

Volkmann, Hefter, Lange, & Freund, 1992), and pace stability (Schmitz-Hubsch, Eckert, Schlegel, Klockgether, & Skodda, 2012; Skodda, 2011; Skodda, Flasskamp, & Schlegel, 2010, 2011; Skodda & Schlegel, 2008). The available literature therefore suggests a role for medial premotor areas (both pre-SMA and SMA-proper), prefrontal cortex, and the basal ganglia in the timing of speech actions.

Speech Motor Programming

Once selected, ordered, and precisely timed, speech movements need to be fine-tuned, which includes adjustments of velocity, muscle tone, movement range, and direction, all accomplished within specific phonetic, environmental, emotional, and social contexts. The sensory systems provide information about the initial conditions such that the motor commands for a desired outcome can be successfully achieved given the state of the vocal tract. In each language, a closed set of syllables and phonemes is available. These syllables and phonemes are stored as a set of sensorimotor routines with invariant goals and include information about the proprioceptive, tactile, and auditory feedback associated with each movement. Nevertheless, adjustments to these routines are constantly needed because phonemes, syllables, and words are never produced in an identical manner. Indeed, one important notion for speech production is that of *motor equivalency*, which is the capacity to achieve a movement goal in various ways, from different starting points and under different conditions. A related notion is that of *co-articulation*, which is the temporal-spatial overlap of movements associated with the production of more than one sound occurring at a single point in time (Liberman, Harris, Hoffman, & Griffith, 1957; MacNeilage & DeClerk, 1969). In every language, phonemes in the speech stream have a strong effect on the phonemes that are produced close to them (both before or after) leading to anticipatory and carryover co-articulation effects. This suggests either that motor commands for adjacent vowels and consonants are processed simultaneously, or that plans for moving the articulators (tongue, lips, soft palate, mandible) from one position to the other are established in advance. Because of the speed at which speech is produced, and the difficulty in dissociating motor programming from motor planning steps with current neuroimaging and neuromodulation techniques, little is known about the neural basis of co-articulation processes. According to the model developed by Van Der Merwe (2009), brain regions involved in speech motor programming would include the cerebellum, SMA-proper, M1, and the basal ganglia (especially the putamen), but empirical evidence still awaits, and research is ongoing to provide additional information about the neural underpinning of these important processes.

SPEECH MOVEMENT EXECUTION

Once motor planning and programming is terminated and a trigger for initiation has been generated, the execution of speech movements begins. Understanding the neural basis of speech movement production—including both phonation and articulation—requires an understanding of the central and peripheral nervous system because both are essential to produce speech. Indeed, in addition to the complex organization in the central nervous system (CNS) that we have touched upon in the previous sections, the production of speech sounds requires the orchestration of ~100 striated and visceral muscles located in the abdomen, neck, larynx, pharynx, and oral cavity, which are innervated through six pairs of cranial nerves.

Motor commands for speech are sent to the ventral part of M1v, sometimes referred to as the final common pathway, which contains (most of) the neurons controlling the vocal apparatus (Penfield & Boldrey, 1937). From M1v, the motor commands are sent toward the relevant muscles through the pyramidal system. The pyramidal system is one of the most important efferent pathways for the control of voluntary movements, including speech. It includes two major divisions: the corticospinal and corticobulbar tracts. For speech, the primary division is the corticobulbar one, but both divisions play a part. While the corticospinal tract innervates motor nuclei located in the spinal cord, the corticobulbar tract innervates motor nuclei located in the brainstem. Motor nuclei are collections of neuron bodies in the brainstem and spinal cord that are associated with one or more cranial or spinal nerve nerves, respectively. The pyramidal system serves to connect neurons in the cortex, called the upper motor neurons (UMNs), to neurons located in the brainstem (forming the corticobulbar tract) and spinal cord (forming the corticospinal tract), which are called lower motor neurons (LMNs). That is, UMNs in the cortex do not directly connect to the muscles. It is the LMNs that innervate the muscle fibers located in the face, neck, and abdomen.

M1 is the cortical area that contains the largest number of pyramidal neurons (Kuypers, 1973; Murray & Coulter, 1981; Ralston & Ralston, 1985), in particular, the giant Betz cells located in cortical layer V. However, it is not the only cortical area that projects to LMNs. Indeed, anatomical studies have shown that other cortical areas contain a high density of neurons directly projecting to LMNs (for a review of the connectivity of non-primary motor areas, see Picard & Strick, 1996, 2001). These are the same regions that are directly connected to M1 through long and short association fibers: the SMA (Dum & Strick, 1991, 1996; Muakkassa & Strick, 1979), the CMA located just beneath the SMA on the dorsal and ventral banks of the cingulate sulcus (Dum & Strick, 1991; Muakkassa & Strick, 1979), the PMd and the PMv (Barbas & Pandya, 1987; He, Dum, & Strick, 1993). For example, electrical stimulation of the SMA (Fried et al., 1991; Penfield & Welch, 1951; Talairach & Bancaud, 1966) and CMA (von Cramon & Jurgens, 1983) induces vocalization and speech arrest in humans, suggesting a role in the control of phonation and articulation for these regions. This means that premotor areas have some level of direct control over the generation and control of movement, independently of M1v (Dum & Strick, 1991). Axons originating from M1v, SMA, CMA, and PMv are arranged in a fan-shaped collection of axons that is directed downward toward the brainstem. At the level of the thalamus and basal ganglia, the axons are compacted into a dense band of axons, which is known as the *internal capsule* and within which axons originating from different locations are segregated (Beevor & Horsley, 1890; Dejerine, 1901). Most corticobulbar axons are located in the genu of the internal capsule, while corticospinal axons are located in the posterior limb of the internal capsule. Because all the projections to and from the cortex go through the internal capsule, even small lesions can produce widespread motor deficits, including speech deficits, particularly if the lesion occurs in the genu of the internal capsule. Most pyramidal axons cross from one hemisphere to the other before entering the spinal cord at the level of the medulla oblongata (i.e., the pyramidal decussation). Corticobulbar axons also cross at the level of the brainstem, though there is substantial bilateral innervation of the cranial nerve (CN) motor nuclei, making the speech system fairly resistant to unilateral UMN damages. The exceptions include contralateral innervation of ventral cell groups of the motor nucleus of the facial nerve (CN VII), and the hypoglossal nucleus (CN XII).

The production of speech and voice depends upon the integrity of both the corticospinal tract, which innervates the muscles of respiration located in the abdomen, neck, and shoulder, and the corticobulbar tract, for the innervation of laryngeal and supra-laryngeal muscles (for reviews, see Jurgens, 2002, 2009). Six pairs of cranial nerves are involved: (1) the trigeminal nerve (CN V), which controls the muscles of mastication (jaw) (important for articulation) and carries general sensory information from the pharynx and anterior two-third of the tongue; (2) the facial nerve (CN VII), which controls muscles of facial expression (e.g., those controlling the lips) and eye movements; (3) the glossopharyngeal nerve (CN IX), which controls the stylopharyngeus muscle (which elevates the pharynx during speech and swallowing) and carries general sensory information from the face and posterior one-third of the tongue; (4) the vagus nerve (CN X), which controls muscles of the larynx and pharynx and carries general sensory information from the larynx; (5) the accessory nerve (CN XI), which controls the sternomastoid (head rotation and chin elevation) and trapezius muscle; and, finally, (6) the hypoglossal nerve (CN XII), which controls intrinsic and extrinsic tongue muscles (except the palatoglossus).

Another peculiarity of the speech system is that some of its components are under dual control (voluntary and autonomous). The autonomous pathway involves the anterior cingulate cortex (ACC), the periaqueductal gray matter (PAG), and the reticular formation (Jurgens, 2002, 2009; von Cramon & Jurgens, 1983). This pathway is important for the innate control of nonverbal and emotional vocalizations (e.g., crying, laughing, and moaning) (Scheiner, Hammerschmidt, Jurgens, & Zwirner, 2004). Vocalizations can also occur without a cortical intervention through the reticular formation's connection to brainstem motoneurons. Interestingly, unlike humans, other mammals lack a direct control of M1 on laryngeal motoneurons. In mammals, M1 connects to the laryngeal motoneurons indirectly through the reticular formation (Jurgens, 2009; Simonyan & Jurgens, 2003). In addition to these two pathways, it is worth mentioning that there are other connections, often called *extrapyramidal* or *indirect*, between the cortex, the reticular formation, and laryngeal motoneurons in the brainstem (see Figure 15.1 for an overview of these connections). These extrapyramidal pathways link the cortex, including M1v, premotor, and sensory areas, with brainstem nuclei, in particular the reticular formation (through the corticoreticular tract), which in turn modulate laryngeal motoneurons in the brainstem. Though the roles of these pathways have not been completely elucidated, they would be involved in controlling posture and muscle tone, thus providing a framework upon which voluntary speech movements can take place. They may also play a role in coordinating reflect activities within different cranial nerves.

SENSORIMOTOR INTEGRATION

Sensory and motor systems for speech are constantly interacting, and sensorimotor integration is key to successful and efficient speech production. There is strong empirical evidence that the unanticipated alteration of auditory and somatosensory feedback during speech production can lead to compensatory movement adjustments, which show the importance of sensory feedback for speech motor control. Indeed, compensatory movements have been shown following unanticipated alteration of auditory feedback for pitch (Burnett, Freedland, Larson, & Hain, 1998; Jones & Munhall, 2000), and vowel formants (Purcell & Munhall, 2006a, 2006b), as well as for unexpected perturbation of lip or jaw movements (Abbs, Gracco, & Cole, 1984; Ito, Kimura, & Gomi, 2005; Tremblay et al., 2003).

Though sensory feedback is important for speech motor control, if all movement adjustments depended solely on afferent sensory (external) feedback, speech motor control would be inefficient because of the delay involved in receiving and processing this information as it takes about 100 milliseconds for the auditory signal to reach the auditory association areas. The speech production system therefore also relies upon predictive feedforward processes for movement control. When a speech act is ready to be produced, a copy of the prepared motor commands, the *efference copy*, or *corollary discharge* (Sperry, 1950; Von Holst & Mittelstaedt, 1973), is sent to an internal model of the vocal tract to predict movement sensory consequences, while in parallel a copy is sent through the descending pathway to the muscles involved. The efference copy signal inhibits activation of the STGp, which results in a phenomenon referred to as *speech-induced suppression* in which the auditory cortex responds less to speaking than to hearing a recording of a similar utterance (Christoffels, van de Ven, Waldorp, Formisano, & Schiller, 2011; Eliades & Wang, 2003; Houde, Nagarajan, Sekihara, & Merzenich, 2002; Meekings et al., 2016). The internal model is useful for online movement control because the sensory consequences of a movement command can be evaluated and corrected even before external feedback has reached the central nervous system. When a mismatch is detected between expected and planned sensory consequences, an error signal is generated. fMRI studies of altered auditory feedback have shown an increased activation in the superior temporal cortex in the presence of altered feedback compared to unaltered feedback (Christoffels et al., 2011; Meekings et al., 2016; Tourville, Reilly, & Guenther, 2008), suggesting that the error signal is generated in the superior temporal cortex. Similar mechanisms would exist for the somatosensory modality as well. According to Houde and Nagarajan (2011), the signal to correct the motor commands is sent from the temporal cortex to M1v through PMv, which is connected to both somatosensory areas, including area SII (Matelli, Camarda., Glickstein, & Rizzolatti, 1986) and the STGp (Chavis & Pandya, 1976; Schmahmann et al., 2007).

Most models of speech production acknowledge a role for both external and internal feedback in speech motor control. External feedback is critical to learn the relationship between motor commands and their sensory consequences (the internal model), to continuously update the internal model and to detect and correct for sudden perturbations (Hickok, 2014), while internal feedback is critical for fast online adjustments.

White Matter Cortical and Subcortical Tracks and Articulation

Given the complexity of the speech production system, vast networks of fiber pathways are required to support speech processes, which can be together considered as part of three speech streams: (1) a *dorsal speech stream* also involved in speech perception and sensorimotor integration (Hickok & Poeppel, 2007; see Hickok, Chapter 20 in this volume); (2) a *ventral stream* also involved in semantic processing (Hickok & Poeppel, 2007); and (3) a *motor-speech stream* involved in the implementation of phonation, articulation, and resonance (Dick, Bernal, & Tremblay, 2014). These fiber pathways (see Figure 15.2 for an overview) include (1) long-association cortical fiber pathways, comprising the superior longitudinal/arcuate fasciculus (SLF/AF), the frontal aslant tract (FAT), and cortico-striatal fibers (including the external capsule, and fronto-striatal tract or subcallosal fasciculus of Muratoff [i.e., the Muratoff bundle]); (2) the descending motor tracts, especially the corticobulbar pathway; and (3) the cortico-ponto-cerebellar system.

Long Association Cortical Pathways for Speech Production

Superior Longitudinal/Arcuate Fasciculus

The SLF/AF is the most prominent fiber pathway associated with speech and language. Historically, the SLA/AF was proposed to connect the posterior IFG with the inferior parietal lobule (including the supramarginal gyrus) and posterior superior middle temporal gyrus/sulcus (MTG/MTS) (von Monakow, 1897; Wernicke, 1874). However, the anatomical connectivity of this pathway has been re-evaluated in recent years, and it is now thought that the SLF/AF can be differentiated into several subcomponents. For example, research in macaque suggests that the SLF/AF can be differentiated into four subcomponents (SLF I, II, III, and AF) (Schmahmann & Pandya, 2006; Yeterian,

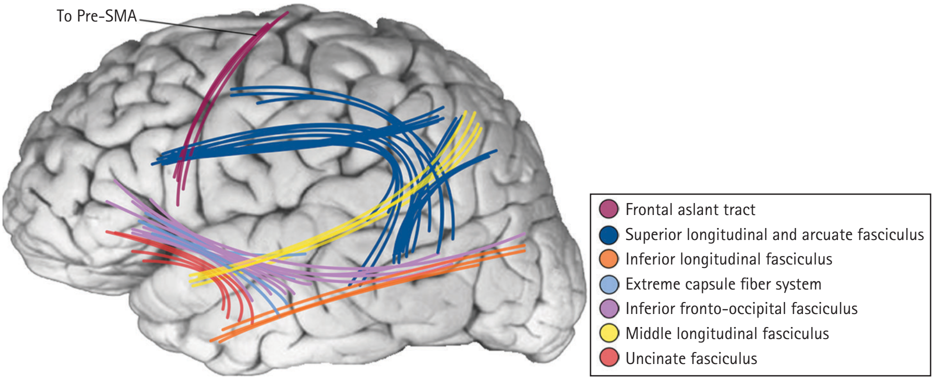
To Pre-SMA
● Frontal aslant tract
● Superior longitudinal and arcuate fasciculus
● Inferior longitudinal fasciculus
● Extreme capsule fiber system
● Inferior fronto-occipital fasciculus
● Middle longitudinal fasciculus
● Uncinate fasciculus

FIGURE 15.2. Long association fiber pathways of the perisylvian cortex. The superior longitudinal and arcuate fasciculus are the major fibers of the dorsal stream, while the inferior longitudinal fasciculus, extreme capsule fiber system, inferior fronto-occipital fasciculus, middle longitudinal fasciculus, and uncinate fasciculus comprise the ventral stream. The frontal aslant tract connects the pre-SMA with the pars opercularis of the IFG.

Pandya, Tomaiuolo, & Petrides, 2011). Within this parcellation, the SLF III and AF components are the components most likely involved in articulation. In the macaque, the SLF III is a parieto-frontal pathway connecting the anterior inferior parietal lobule with the PMv and posterior IFG. In contrast, the AF component is a temporo-premotor pathway thought to connect the STGp with more dorsal premotor and lateral prefrontal cortex (areas 9/46d, 8Ad, and 6d), though not to the IFG (Schmahmann & Pandya, 2006), as previously believed.

In contrast to the macaque data, however, other models based on diffusion-weighted imaging of the human brain do support direct temporo-inferior frontal connectivity in humans (Bernal & Altman, 2010; Brauer, Anwander, Perani, & Friederici, 2013; Brown et al., 2013; Catani et al., 2005; Glasser & Rilling, 2008; Makris et al., 2005; Patterson, Van Petten, Beeson, Rapcsak, & Plante, 2014; Perani et al., 2011; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). Given the inability of nonhuman primates to speak naturally, it is possible that the connectivity of this pathway may differ between species. In Catani's influential model, the "long (direct) segment" of the SLF connects the posterior superior temporal, middle, and inferior temporal gyrus with the IFG (*pars triangularis* and *pars opercularis*) and PMv (see Catani & Forkel, Chapter 9 in this volume). This is closer to the classical definition of the SLF/AF. Two "indirect" segments are also identified in this model: anterior and posterior. The anterior part is a fronto-inferior parietal-posterior temporal segment, and can be considered to constitute the SLF III. A posterior part constitutes a posterior temporal-inferior parietal segment (Catani et al., 2005; Martino et al., 2013).

Because of the connectivity between posterior IFG and supramarginal gyrus, the anterior component may be an important component of the articulatory loop. Electrostimulation of the white matter underneath the IFG and IPL/pSTG results in speech arrest/articulation disturbance (Duffau et al., 2002; Duffau, Gatignol, Denvil, Lopes, & Capelle, 2003; Maldonado et al., 2011), and damage to the pathway is associated with transient dysarthria (Duffau et al., 2003; see, in this volume, Duffau, Chapter 8, and Ziegler, Schölderle, Aichert, & Staiger, Chapter 18). A number of studies have suggested that the white matter of the long segment and the anterior segment is related to speech articulation/speech fluency. For example, measures of fluency (Marchina et al., 2011; Tanabe et al., 1987) and verbal repetition (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Fridriksson et al., 2010) in people with left hemisphere stroke are associated with white matter damage to these pathways.

The involvement of the ventral stream in speech production is less well established, but if it is involved in speech production it is likely supporting semantic processing. According to a recent computational model (called Lichtheim 2; Ueno, Saito, Rogers, & Lambon Ralph, 2011), this is the presumed pathway, via the left uncinate fasciculus (UF) and left extreme capsule fiber system (EmC-fs), by which meaning is mapped to articulation. Damage to this pathway is mainly associated with deficits in naming famous faces (Papagno et al., 2011), which fits with the model's predictions. However, this proposal is disputed by another model, the Weaver++/ARC model (Roelofs, 2014). These authors suggest that the dorsal stream involvement is the primary pathway in speech production. Roelofs points to data showing that production impairments are more associated with damage to the left AF than to damage to the ventral pathways (namely, UF; Marchina et al., 2011; Wang, Marchina, Norton, Wan, & Schlaug, 2013). Another pathway that may play a role in semantic memory and semantic processing during speech production is the inferior fronto-occipital fasciculus (IFOF; de Zubicaray, Rose, & McMahon, 2011; Duffau et al., 2005; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). The IFOF originates in the inferior and medial occipital lobe (and possibly the medial parietal lobe), sends projections to the ventral temporal lobe, travels through the temporal stem dorsal to the UF, and projects to the IFG, the medial and orbital frontal cortex, and the frontal pole (Catani et al., 2003). Connectivity of the temporal and frontal lobes, and its importance for speech, remains an area of intense research.

The Frontal Aslant Tract

Although it does not appear in historical atlases of white matter, the frontal aslant tract (FAT) has been recently identified using diffusion weighted imaging in humans (Broce, Bernal, Altman, Tremblay, & Dick, 2015; Catani et al., 2012b; Catani et al., 2013; Ford, McGregor, Case, Crosson, & White, 2010; Henry, Berman, Nagarajan, Mukherjee, & Berger, 2004; Kinoshita et al., 2014; Klein et al., 2007; Lawes et al., 2008; Oishi et al., 2008; Vergani et al., 2014). As shown in Figure 15.3, the FAT runs obliquely (aslant) from lateral to medial cortex, and is proposed to connect the posterior IFG, *pars opercularis*, to the pre-SMA and (to a lesser degree) the SMA-proper. This connectivity profile is consistent with a number of emerging studies of the functional association between the FAT and speech. For example, Catani and colleagues (2013) reported that reduced integrity of the FAT is associated with decreased verbal fluency in people with primary progressive aphasia (PPA). In a case study using both electrostimulation and diffusion tensor

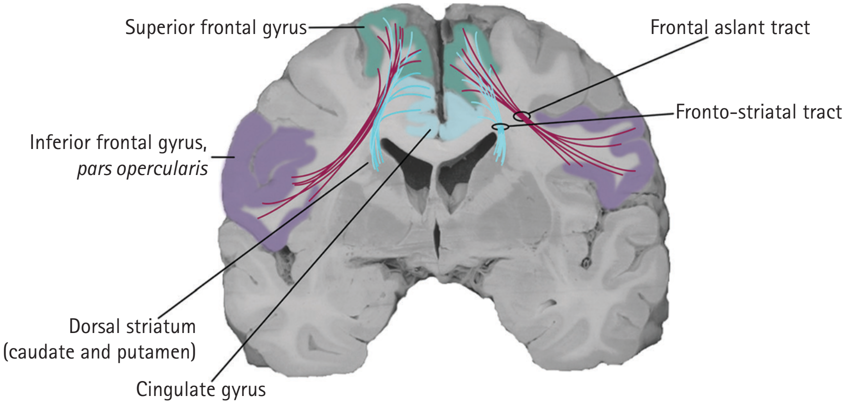
Superior frontal gyrus
Frontal aslant tract
Fronto-striatal tract
Inferior frontal gyrus, *pars opercularis*
Dorsal striatum (caudate and putamen)
Cingulate gyrus

FIGURE 15.3. Connectivity of the frontal aslant and fronto-striatal tracts. The frontal aslant tract connects pre-supplementary motor area (pre-SMA) with the IFG, *pars opercularis*. The dorsal striatum (caudate and putamen) has dense connectivity with the SMA and CMA, in addition to other frontal (dorsolateral and orbitofrontal) projections not shown. Cortico-striatal connectivity is also supported by fibers of the external capsule (not shown).

imaging (DTI), Vassal and colleagues (Vassal, Boutet, Lemaire, & Nuti, 2014) showed that stimulation of the left FAT induced speech arrest, with normalization of speech occurring when stimulation stopped. Kinoshita and colleagues (2014) also used both electrostimulation and DTI in 19 participants, and showed that electrostimulation of the left, but not the right, FAT induced speech arrest. Finally, emerging evidence suggests that this tract is associated with stuttering (Kemerdere et al., 2016; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016; see Ziegler, Schölderle, Aichert, & Staiger, Chapter 18 in this volume). The evidence thus suggests that the FAT is a tract that can be reliably identified, and that it has a functional relevance to the production of speech. For a full review of the FAT, refer to Dick et al (2018)

Fronto-Striatal Pathways: External Capsule and Subcallosal Fasciculus of Muratoff (Muratoff Bundle, or Fronto-Striatal Tract)

The medial frontal cortex makes connections with the dorsal striatum, and planning and execution of fluent speech relies on the integrity of these cortico-striatal pathways (Civier, Bullock, Max, & Guenther, 2013). There are at least two fiber bundles important for these cortico-striatal connections. Primary and non-primary motor areas connect to the posterior third of the striatum (particularly the posterior putamen), and travel mainly in the external capsule (Schmahmann & Pandya, 2006). After targeting the putamen and caudate nuclei, connections are established with the external and internal pallidum, subthalamic nucleus, and ventrolateral thalamic nuclei. The ventrolateral thalamic nuclei project back to primary and nonprimary cortical motor areas, forming the motor component ("motor loop") of the cortico-striatal circuit. The pre-SMA, in contrast, along with prefrontal cortex, connects to more anterior parts of the striatum, also via the external capsule. From there, these regions target the internal pallidum, and the ventral anterior thalamic nuclei, which in turn projects back to these same cortical areas, forming a cortico-striatal loop. In addition to the external capsule, the fronto-striatal tract (FST; Kinoshita et al., 2014; Lehéricy et al., 2004a; Lehéricy et al., 2004b), essentially the frontal component of the subcallosal fasciculus of Muratoff (Muratoff bundle), has received more recent interest. It is more easily detected in the macaque, and can be differentiated reliably from the fronto-occipital-fasciculus (Schmahmann & Pandya, 2006). Yet, Kinoshita and colleagues (2014) reported successful tractography in patients undergoing awake surgery for tumor resection, and also showed that stimulation of the pathway (namely caudate-pre-SMA connections) evokes motor initiation impairment and speech disturbances. Thus, fibers traveling in this pathway may be important for speech.

Cortico-Cerebello-Cortico Loops

The majority of the afferent connections to the cerebellum are conveyed through the middle and inferior cerebellar peduncles, while the majority of the efferent fibers travel via the superior cerebellar peduncle. Major inputs from the cortex travel via various pontine nuclei, where almost all the cortico-ponto-cerebellar fibers cross the midline in the basal pons to terminate in the contralateral half of the cerebellar cortex. The cerebellum itself projects to primary and nonprimary motor areas and to the prefrontal cortex (including the pre-SMA) through projections from the cerebellar dentate nucleus via the ventrolateral nucleus of the thalamus, which projects to the contralateral primary and nonprimary motor areas and prefrontal cortex (Salmi et al., 2010). These connections form a cortico-cerbello-cortical loop involved in the control of actions in general, including speech. Empirical studies indicate that cerebellar lesions impact speech and language function (Fiez, Petersen, Cheney, & Raichle, 1992 Vias & Dick (2017)). Fluency deficits in both semantic (category) and letter fluency tasks are observed in adult patients with focal and degenerative cerebellar pathologies (Akshoomoff, Courchesne, Press, & Iragui, 1992; Appollonio, Grafman, Schwartz, Massaquoi, & Hallett, 1993; Leggio, Silveri, Petrosini, & Molinari, 2000; Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000; Richter et al., 2007; Schweizer et al., 2010).

Summary

Many fiber pathways support the production of speech, integrating information from large segments of the cortex, basal ganglia, thalamus, and cerebellum. The importance of the basal ganglia and cerebellum to speech production has been known for some time (Robin & Schienberg, 1990; see, in this volume, Ziegler, Schölderle, Aichert, & Staiger, Chapter 18, and Copland & Angwin, Chapter 33), but the study of the particular fiber pathways supporting the communication among these regions, using newly established methodologies such as diffusion-weighted imaging or connectivity modeling, is a more recent phenomenon (Manes et al., 2014). What this brief review has hopefully accomplished is to reinforce that these fiber pathways should be understood as part of a distributed network supporting speech production, and attempts should be made to study them as such.

CONCLUSIONS

In this chapter, we have reviewed the neural systems that controls speech production at all levels of the nervous system, from a complex web of cortical regions such as M1v, PMv, SMA, pre-SMA, CMA, and the insula, interconnected through both short- and long-association pathways, all the way down to the cranial nerve nuclei in the brainstem through the corticobulbar tract. We have seen that loops of internal control involving the basal ganglia, thalamus, and cerebellum are also involved in speech movement preparation, including sequencing and motor timing. Though several aspects of speech motor-control processes remain to be clarified, such as motor programming and co-articulation, it is clear that the advent of multimodal imaging and brain stimulation techniques have allowed us to make major strides toward understanding the neural basis of human communication, one of the most distinctive features of our species.

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CHAPTER 16

THE NEURAL ORGANIZATION OF SIGNED LANGUAGE

Aphasia and Neuroscience Evidence

DAVID P. CORINA AND LAUREL A. LAWYER

Introduction

Signed languages used in Deaf communities are naturally occurring human languages that exhibit the full range of linguistic complexity found in spoken languages (see Newman, Chapter 14 in this volume). Just as there are a multitude of spoken language communities around the world (e.g., speakers of Farsi/Persian, Thai, German, and English), there are also many distinct sign language communities (e.g., signers of Taiwan Ziran Shouyu [TZS], Deutsche Gebärdensprache [DGS], Lengua de Sigños Española [LSE], and British Sign Language [BSL], to name but a few). Although the histories and geographies of signed languages are less well documented, it is known that signed languages arise spontaneously, over several generations, from isolated communities that have a preponderance of deaf individuals. Such situations are not as rare as one might think, as genetic influences on the transmission of deafness are well attested (Groce, 1985; Sandler, Meir, Padden, & Arnoff, 2005).

Despite the widespread use of signed languages in Deaf communities, most neurobiological models of language processing have been predicated on research using spoken languages only. Neurolinguistic studies using signed languages provide a unique opportunity to distinguish neurobiological substrates that universally support language processing from those that are dependent on aural-oral processes. Studies of sign language processing in the adult brain highlight a largely modality-independent language system, with some important distinctions. These differences can largely be traced to perceptual processes related to the modality of the language itself (visuospatial as opposed to auditory). The following review will address the ways in which sign-language research broadly supports current views of language processing in a modality-independent manner, before turning to several areas in which sign-language processing differs from spoken-language processing. Finally, we conclude with two areas in which sign language has bearing on current issues in neurolinguistics: the profile of neurodegenerative diseases and their effect on signing, and the relationship between sign perception and human action understanding.

LANGUAGE PROCESSING IS PRIMARILY MODALITY-INDEPENDENT

Evidence from Sign Language Aphasia

Deaf signers, like hearing speakers, exhibit distinct language disturbances when cortical regions are damaged. Neurolinguistic studies of lifelong signers whose primary and preferred mode is a signed language have documented patterns of sign-language disturbances following acute brain damage and have helped to identify brain regions that are critical for sign-language processing. These studies indicate remarkable parallels between left hemisphere regions that support spoken-language processing and those that support signed-language processing. Sign-language disturbances vary systematically depending on the locus of the lesion (Hickok, Love-Geffen, & Klima, 2002; Marshall, Atkinson, Smulovitch, Thacker, & Woll, 2004; Poziner, Bellugi, & Klima, 1987; for a review see Corina, 1998a, 1998b), supporting long-standing generalizations regarding differential contributions of left hemisphere anterior-frontal and posterior-temporal regions in language processing. In the following, we review the details of several case studies that provide support for this analysis.

Broca-Like Signing

In spoken language, language production impairments are typically associated with lesions that involve the lower posterior portion of the left frontal lobe (e.g., Broca's area, Brodmann area 44/45) and often extend into the periventricular white matter (cf. Goodglass, 1993; Mohr et al., 1978; see Wilson, Chapter 2 in this volume). Two well-documented cases of sign language aphasia provide additional support for the critical role that left frontal regions play in language production.

Patient G. D., reported in Poizner et al. (1987), an active mother married to a deaf signing man with three deaf signing children, had a large lesion to left frontal areas that encompassed traditional Broca's territory (including BA 44/45), resulting in a profound expressive aphasia. The patient presented with halting dysfluent sign articulation and an agrammatic language profile. In particular, American Sign Language (ASL) sentence structure was greatly simplified (i.e., telegraphic), and signs did not include the required movement modulations that signal morpho-syntactic inflection. In contrast to her expressive deficits, G. D.'s comprehension was well within normal limits.

Patient R. S., reported in Hickok, Kritchevsky, Bellugi, and Klima (1996), is a native signer, who learned ASL in infancy from her deaf signing parents. She had a left inferior frontal lesion that was more restricted to classically defined Broca's territory. This lesion involved inferior motor cortex, most of the pars opercularis, and anterior, superior insula. Subcortically, this lesion also undercut most of the pars triangularis and the lower motor cortex. During the acute phase of this stroke, the patient showed a marked expressive aphasia with nonfluent, effortful production, which also effected sign repetition. Sign language comprehension, however, was intact. Over time, the expressive aphasia largely resolved, though word-finding difficulties remained.

R. S. exhibited an unusual paraphasia restricted to two-handed signs. In signs that require two hands to move independently, R. S. would move one of her hands incorrectly. In other cases, R. S. would fail to preserve the required spatial relationships between the two hands. Moreover, during one-handed signing, R. S. mirrored the movements and handshapes of the dominant hand on the nondominant hand, but somewhat reduced in degree of movement. This mirroring was not seen during nonlinguistic movements and appears different from pathological mirror movements seen in some cases of hemiparesis. This case illustrates that the modality of the linguistic system can place unique demands on the neural mediation and implementation of language. These errors may be taken as evidence of modality-dependent linguistic impairment.

Wernicke-Like Signing

Spoken language comprehension deficits are well attested after left hemisphere temporal lobe damage (cf. Damasio, 1992; Dronkers & Baldo, 2009; Naeser, Helm-Estabrooks, Haas, Auerbach, & Srinivasan, 1987). Wernicke's aphasia, which is expressed as impaired language comprehension accompanied with fluent, but often paraphasic (semantic and phonemic) output, is often associated with damage to the posterior regions of the left superior temporal gyrus. More recent work has suggested the contribution of the posterior middle temporal gyrus in cases of chronic Wernicke's aphasia (Dronkers, Redfren, & Knight, 2000; Dronkers, Redfern, & Ludy, 1995; see Wilson, Chapter 2 in this volume). In two group-level analyses, one on American Sign Language and one on British Sign Language (BSL; a completely distinct language from ASL), damage to the left hemisphere was observed to factor in sign-comprehension deficits as well (Atkinson, Marshall, Woll, & Thacker, 2005; Hickok et al., 2002).

Case studies of signers with damage in parietal areas evidence fluent sign aphasia with associated comprehension deficits, as is also seen in spoken language users. One such example is patient L. K., described in Chiarello, Knight, and Mandell (1982) and in Poizner et al. (1987), who had a left anterior parietal lesion in the region of the supramarginal and angular gyri, but which spared both inferior frontal areas (BA 44/45) and the posterior superior temporal plane (BA 41, 42, and 22). The patient presented with fluid, facile signing, but with phonemic paraphasias and severe anomia. L. K. showed difficulty in grasping test instructions and was unable to carry out 2- or 3-part commands. The patient experienced profound and lasting sign comprehension impairment.

Patient P. D., reported in Poizner et al. (1987), also had a left subcortical lesion with an anterior focus deep to Broca's area, with posterior extension into the white matter underlying the supramarginal and angular gryi. His signing, while fluent, exhibited a number of semantic paraphasias, such as signing "bed" for "chair," "daughter" for "son," and "quit" for "depart." In addition, he produced grammatically inappropriate signs (paragrammatism), and his expression of sentence-level grammatical roles was impaired. Notably, P. D. showed a lack of consistency in spatial agreement required of ASL syntax (Bellugi, Poizner, & Klima, 1989). That is, he would establish nominal referents in space, but he was inconsistent in maintaining co-reference to these previously established locations.

As with the case studies presented in the preceding discussion, the group analysis by Hickok et al. (2002) highlights the role of the left posterior temporal lobe in sign comprehension deficits. There is, however, some controversy over the degree of anatomical overlap between signers with comprehension deficits and users of spoken language who present with Wernicke's aphasia, as others have remarked on the potentially unique role of the left inferior parietal region in sign processing (Corina, 1998a, 1998b; Corina, Lawyer, Hauser, & Hirshorn, 2013; Chiarello et al., 1982; Leischner, 1943; Poizner et al., 1987). For instance, patient W. L. (Corina et al., 1992) exhibited fluent aphasia with severe comprehension deficits, in addition to producing numerous phonemic errors, nearly all of which were errors involving substitutions of handshape. For example, he produced the sign "sister" with an F handshape rather than the required L handshape. The lesion in this case did not include classic Wernicke's area, but rather undercut both frontal and inferior parietal areas, including the supramarginal gyrus. Based on cases such as this, some have suggested that sign-language comprehension may be more dependent than speech on left hemisphere inferior parietal areas, traditionally associated with somatosensory and visual motor integration, while spoken-language comprehension might weigh more heavily on posterior temporal lobe association regions whose input includes networks intimately involved with auditory speech processing (Corina, Lawyer, & Cates, 2012).

Evidence from Cortical Stimulation Mapping

Data from rare clinical cases of cortical stimulation mapping (CSM; see Duffau, Chapter 8 in this volume) performed in deaf and signing neurosurgical patients provide further clues to neural regions that contribute differentially to the patterns of deficits outlined in the preceding. Corina et al. (1999) report the effects of left hemisphere cortical stimulation on sign-language production in a deaf individual, patient S. T., undergoing an awake CSM procedure. Stimulation to two anatomical sites, one in the frontal opercular region of Broca's area (BA 44) and one in the parietal operculum, both led to consistent naming disruptions. However, the errors were qualitatively different.

Stimulation to the frontal opercular region resulted in errors involving the motor execution of signs. These errors were characterized by a lax articulation of the intended sign, with nonspecific movements (repeated tapping or rubbing) and a reduction in handshape configurations to a lax closed fist handshape. These types of errors were observed during trials of both sign and non-sign repetition. These results suggest that the posterior portion of Broca's area is involved in the motoric execution of complex articulatory forms, especially those underlying the phonetic level of language structure (see Tremblay, Deschamps, & Dick, Chapter 15 in this volume).

The sign errors observed with stimulation to the supramarginal gyrus (SMG) (BA40) resulted in both formational and semantic errors. Formational errors were characterized by repeated attempts to articulate the intended targets, and successive approximations of the target sign were common. Notably, we do not find the lax and reduced articulations characteristic of the signs seen with stimulation to Broca's area. Semantic errors were also observed with stimulation to the SMG. Interestingly, many of these errors involve semantic substitutions that were formationally similar to the intended targets. As these errors did not affect non-signs, this suggests that the SMG plays a critical role in the selection of the individual semantic and phonological (i.e., handshape, movement, and, to a lesser extent, location) components of sign forms.

Evidence from Neuroimaging Studies

Early functional imaging studies often emphasized the overlap of activation between regions subserving sign processing and those regions traditionally thought to mediate speech processing (cf. Bavelier et al., 1998; McGuire et al., 1997; Neville et al., 1998; Nishimura et al., 1999; Petitto et al., 2000; Soderfeldt et al., 1997). For example, Pettito et al. (2000) and McGuire et al. (1997) reported significant activation in left inferior frontal regions, specifically Broca's area (BA 44 and 45), and anterior insula during overt and covert tasks of sign generation. Subsequent work using more refined cytoarchitectonic references have indicated that BA 45 is activated during both sign and speech, and can be differentiated from complex oral/laryngeal and limb movements, which result in more ventral activation of BA 44. This interpretation accords well with the cortical stimulation finding reported in Corina et al. (1999). Overall this research speaks to the modality independence of the pars triangularis (BA 45) (Horowitz et al., 2003), a region that has been traditionally considered a "speech-motor" region.

Neuroimaging studies of sign-language production reveal further commonalities in the neural systems underlying core properties of language function in sign and speech. In studies of ASL verb generation, in which patients are required to generate a verb in response to a given noun, José-Robertson et al. (2004) reported left-lateralized activation within perisylvian frontal and subcortical regions commonly observed in spoken-language generation tasks. In an extension of this work, Corina, San José-Robertson, Guillemin, High, and Braun (2003) reported that the left-lateralized pattern was not significantly different when the production of a repeat-generate task was conducted with a signer's right/dominant or left/nondominant hand. This finding is also consistent with the observation that aphasic deficits in right-handed signers are often realized on the ipsilesional limb (i.e., the left hand in cases of left hemisphere damage), indicating that the observed errors are not an artifact of motoric weakness, but rather a central disorder of linguistic control mediated by the left hemisphere.

In a large-scale analysis of deaf signers and hearing non-signers engaged in object-naming tasks, Emmorey, Mehta, and Grabowski (2007) reported areas of overlap in neural activation for sign production in deaf participants and word production in hearing participants. This analysis identified regions supporting modality-independent lexical access. Common regions included the left medial temporal cortex and the left inferior frontal gyrus. Emmorey et al. (2007) suggest that left temporal activation reflects conceptually driven lexical access (Indefrey & Levelt, 2004; see de Zubicaray & Piai, Chapter 19 in this volume). In this view, for both speakers and signers, activation within the left inferior temporal gyrus may reflect pre-lexical conceptual processing of the pictures to be named, while activation within the more middle temporal regions may reflect lemma selection prior to phonological code retrieval. These results argue for a modality-independent fronto-temporal network that subserves both sign and word production.

Subcortical Impairments

While previous aphasia and neuroimaging studies have done an admirable job in describing the commonalities in cortical regions between users of signed and spoken languages, more recent studies have begun to expand our knowledge of the contributions of subcortical structures on signing. For instance, Corina et al. (2014) present contrasting profiles of two patients with damage to left hemisphere subcortical regions. Patient O. S. had damage to the left putamen/basal ganglia and anterior striatal-subcortical white matter regions. O.S. exhibited a Wernicke-like aphasia, with notably hypokinetic signing. In this case, articulatory precision was compromised, evincing reduced movement, and a lack of differentiation between lexical and transitional movements in signing. Patient D.T., on the other hand, had a lesion restricted to the left putamen, and showed no evidence of aphasia. However, her signing was hyperkinetic, showing an exuberance of movement, often overshooting and repeating movements, and with inability to dampen contacting movements. She also showed difficulty in right- and left-hand coordination, and had a somewhat flaccid wrist tone. These two case studies provide some of the first evidence for dysarthria in a sign language, and provide evidence for the role of the basal ganglia in the motor execution of signing.

Sign-Language Processing Engages Specialized Cortical Regions

As outlined earlier, studies using a variety of methodologies (aphasia, neuroimaging, cortical stimulation mapping) provide converging evidence for the uniformity of neural systems underlying spoken and signed languages. However, numerous studies have also revealed instances where sign-language processing invokes neural resources that differ from those observed for spoken languages. These instances illuminate the intimate connections between language modality and brain structures that support language processing. In the following, we introduce several research areas that highlight the roles of linguistic modality, sensory experience, and language development, and which underlie the cortical organization of sign language processing.

The Right Hemisphere

The once popular premise that the left hemisphere plays an exclusive role in the processing of spoken language has given way to a more nuanced assessment of the cerebral distribution of language functions (McGettigan & Scott, 2012). While researchers have recognized that the right hemisphere may contribute to extra-linguistic functions such as discourse and pragmatic processes (see Rapp, Chapter 28 in this volume), we also observe new evidence that both hemispheres participate in core aspects of speech perception (see, for example, Poeppel, 2003; Scott, Blank, Rosen, & Wise, 2000; Shalom & Poeppel, 2007; Zatorre & Belin, 2001; see also Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume). Within the realm of sign-language processing there have been many indications that the right hemisphere may also play a heightened role in the mediation of the visuospatial properties of signed languages.

Facial Processing

Imaging studies of sign-language processing have often noted significant right hemisphere activation. For example, activations in right hemisphere superior temporal, inferior frontal, and posterior parietal regions have been reported for sentence-level processing tasks (e.g., MacSweeney et al., 2006; MacSweeney et al., 2002a, 2002b; Neville et al., 1998; Newman, Bavelier, Corina, Jezzard, & Neville, 2002). The question of whether these patterns of activation are unique to sign has been the topic of debate (Corina, Neville, & Bavelier, 1998; Hickok, Bellugi, & Klima, 1998). Mounting evidence suggests that some aspects of this right hemisphere activation may be attributable to the processing of facial information, which factors significantly in the sign signal. Studies of auditory and audiovisual speech have observed right hemisphere activations that appear similar to those reported in signing (Capek et al., 2004; Davis & Johnsrude, 2003; Schlosser, Aoyagi, Fulbright, Gore, & McCarthy, 1998).

Sentence Comprehension

Researchers have speculated that right hemisphere activation (and damage, in cases of aphasia) is associated with the linguistic use of space in sign language.

Signed languages routinely capitalize on the postural properties of the body, the manual articulators, and the spatial affordances of the visual system to convey complex meanings, including grammatical roles (such as subject/object), prepositional meaning, locative relations, and speaker viewpoint in ways that may not have direct parallels in spoken languages.

One area in which spatial processing interacts with the grammar of signed languages comes in the form of so-called classifier constructions. Signed languages are unique in their ability to spatially represent prepositional relationships between objects, such as *on, above, under*, and so on. These concepts are often conveyed via the depiction of the physical relation itself, rather than encoded by a discrete lexical item. Many signed languages express spatial relationships and events in this manner and have discrete inventories of highly productive grammatical forms, often referred to as "classifiers" or "classifier predicates," which participate in a wide range of depictive constructions (Zwitserlood, 2012). The linguistic status of these classifier forms and their conventions of use have important implications for our understanding of the neurolinguistics of signed languages.

For instance, in a positron emission tomography (PET) study by Emmorey et al. (2002), deaf subjects were asked to examine line drawings of two spatially arrayed objects, and to produce either a classifier description or a description of the spatial relationship using ASL lexical prepositions. This study found evidence for right hemisphere SMG activation for both prepositional forms and classifiers compared to object naming; however, the direct comparison between classifier constructions and lexical prepositions revealed only left hemisphere inferior parietal lobule activation. This counterintuitive finding suggests that right hemisphere activation must be related to some common process, perhaps the spatial analysis of the stimulus to be described, rather than a special spatial-linguistic property of ASL classifiers per se.

Data from aphasic signers support these conclusions. Atkinson and colleagues conducted a group study of signers of BSL with damage to the left or right hemisphere (Atkinson et al., 2005). They devised comprehension tests that examined a wide range of sentence types, including tests of classifier placement, orientation, and rotation. Their findings indicated that signers with right hemisphere damage differed from age-matched controls only on tests of locative relationships expressed via classifier constructions, and on classifier placement, orientation, and rotation (see also Hickok, Pickell, Klima, & Bellugi, 2009). As signers with left hemisphere damage exhibited deficits on all comprehension tests, including classifier constructions, this suggests that the comprehension of classifier constructions requires left hemisphere resources as well as intact right hemisphere visuospatial processing mechanisms. Atkinson et al. (2005, p. 247) state, "some people with RH damage can no longer map non-arbitrary sign locations on to real-world spatial positions." That is, in the case of right hemisphere damage, the signers' difficulties stem from a more general *extra-linguistic* visuospatial deficit, rather than linguistic malfunction.

Discourse

Spatial relationships also figure into larger, grammatically determined discourse elements in sign language. An analysis of language use in two right hemisphere lesioned patients, J. H. and D. N. (Emmorey, Corina, & Bellugi, 1995), reveals the subtle way in which spatial processing interacts with discourse content and cohesion.

Patient D. N. had a right hemisphere lesion that was predominantly medial, and involved the upper part of the occipital lobe and superior parietal lobule. In everyday signing and in picture-description tasks, D. N. showed a pattern of language disruption that affected discourse cohesion via impaired spatial indexing abilities. Spatial indexing is a commonly used device for pronominal reference in signed languages. Signers will point to the spatial location of a previously signed nominal, effectively re-referencing this previously introduced concept. Although D. N. showed unimpaired spatial indexing abilities within sentences, her use of spatial indexing across sentences was inconsistent; that is, she did not consistently use the same indexic points to refer to individuals throughout a discourse.[1] In order to salvage intelligibility, D. N. used a compensatory strategy in which she restated the noun phrase in each sentence, resulting in an overly repetitive discourse style.

The case study of J. H., a deaf signer with a large right hemisphere lesion involving frontal, temporal and parietal cortex, illustrates yet another pattern in the complex relationship between visuospatial processing sign-language abilities. J. H. had severely compromised visuospatial abilities, but nevertheless exhibited remarkably little impairment in sign-language comprehension (Corina, Kritchevsky, & Bellugi, 1996). J. H. produced occasional nonsequiturs and showed abnormal attention to detail—behaviors that are typically found in the discourse of hearing patients with right hemisphere lesions. J. H. also exhibited persistent left-neglect, such that if two identical objects were presented for identification, one in the left visual field and the other in the right visual field, J. H. would show consistent *extinction* for the physical object in his left visual field (see Corina et al., 1996, for a discussion). Despite this, J. H. showed little to no evidence that this visuospatial neglect affected his perception of ASL. Formal testing showed that even in cases of face-to-face signing, where the perception of a two-handed sign such as "deer" (the right and left hands, finger spread, are placed on each side of the forehead like antlers) could easily be perceived as the well-formed one-handed sign "father" (only the dominant hand, fingers spread, is placed in the forehead), J. H. faithfully reports "deer." It is speculated that J. H. was able to use tacit representational knowledge of ASL formational constraints on two-handed signs to process the otherwise neglected information. Similar interactions between abstract lexical representations and attentional neglect have been reported in some neglect-dyslexics (Behrmann, Moscovitch, Black, & Mozer, 1990).

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[1] Contrast this impairment with previously discussed patient P. D., who had left hemisphere damage and showed a lack of spatial agreement within single sentences.

MULTILINGUALISM IN THE DEAF COMMUNITY

Bilingualism

A prominent question in the field of neurolinguistics is whether the neural representation of language changes as a function of the number of languages one knows (see Paradis, 2004, for a review; see, in this volume, Green & Kroll, Chapter 11, and Paz-Alonso, Oliver, Quiñones & Carreiras, Chapter 24). This question takes on additional complexities when considering the expression of multilingualism in the Deaf community, particularly as bilingualism is both the norm and quite variable across individuals. Studies of bilingualism in Deaf communities afford unique opportunities to explore the role of language modality in the expression of neural systems and to evaluate issues related to cognitive control across languages and modalities, as well as issues related to delayed language exposure.

Deaf individuals who have been exposed to and acquired a sign language from birth by virtue of having deaf signing parents are referred to as native signers, for whom a sign language is considered their native language (L1). As these signers typically receive significant educational training based on English, they are also in large part bilingual. However, the language that constitutes the second language (L2) varies, from spoken or written English to a second signed language (e.g., DGS). There is also considerable variability in the linguistic competences in L2 regardless of mode of L2 (spoken, cued, written, etc.), as is observed with spoken-language bilinguals.

To date, the majority of studies investigating the neural representation of signed languages have been conducted on deaf native signers. Comparisons between different populations of sign language users are of great interest, however, as they serve to elucidate the role of early language experience and deafness on cortical organization. One primary group of comparison is hearing native signers (i.e., hearing children who have deaf signing parents), who often acquire a sign language as their L1 in conjunction with spoken English. These individuals have been termed "bimodal bilinguals," illustrating the fact that the two languages known are expressed in different modalities.

Neuroimaging studies of hearing native signers indicate considerable overlap in cortical regions that support sign-language and spoken-language comprehension. This observation is consistent with studies of unimodal bilinguals that indicate shared neural systems mediating L1 and L2. However, some differences in the engagement of left and right hemisphere parietal regions have been observed. For instance, MacSweeney et al. (2002b) tested deaf and hearing native signers in a paradigm that utilized BSL sentence contexts that either made use of spatial-topographic signing space or did not require spatial mapping. While native deaf signers showed activation in the right angular gyrus (BA 39) for spatial-topographic sentences, parietal activation in the hearing native signers was modulated by accuracy on the task.

Neville et al. (1998) compared native deaf signers with native hearing signers processing English and ASL sentences. In this case, Neville et al. (1998) report differences in lateralization across the two groups, with hearing native signers more strongly left-lateralized than the deaf signers. Hearing native signers also showed greater activation in posterior parietal regions, for example intraparietal sulcus (IPS) and anterior occipital sulcus, that may be indicative of greater attentional demands and visual-feature processing during the ASL task. This increased processing for the hearing native signers is consistent with the claim that this group may hold English as their dominant language even if exposed to ASL from birth. Both groups also showed considerable precentral and central sulcus activation in the ASL condition, which is not typically observed in studies of spoken language monolinguals. This may be an indication of greater activation of manual, facial, and body-related pre-motor and motor regions during sign comprehension.

Another group comparison is between native deaf signers and deaf sign language users who were exposed to their L1 at a relatively late age, ranging from early childhood to adulthood. These late learners may also have secondary L1 based on explicit and extensive oral English training, though outcomes are variable, and some individuals may stop using spoken English as they grow into young adulthood. There are well-documented consequences of delayed language exposure (Mayberry, 2010; Mayberry & Eichen, 1991). A study by Newman et al. (2002) also finds late exposure to sign language to contribute significantly to cortical organization even within hearing participants. In this study, deaf and hearing native signers, hearing late learners of ASL, and hearing non-signers viewed sign-language sentences and sign gibberish. Deaf and hearing native signers showed significant activation in right hemisphere posterior-parietal and posterior-temporal regions. These activation patterns were not seen in non-signers, nor were they observed in hearing late learners of sign language. A group analysis of hearing participants confirmed that only hearing native users of ASL, but not late learners who had learned ASL after puberty, recruited the right angular gyrus during this task. Newman and colleagues suggested that the activation of this neural region may be a signature of sign language being acquired during the critical period for language.

Finally, data from spoken-language bilinguals strongly argue for distinguishing neural regions serving aspects of language control from those involved in language switching (see Green & Kroll, Chapter 11 in this volume). Some psycholinguistic studies have argued that there remains less potential for modality-based inference in sign-speech bilinguals owing to the difference in input and output modalities (for example, lack of shared phonological representations). Indeed, Emmorey et al. (2008) report that bimodal bilinguals fail to show enhancements in executive control that are claimed to arise from implicit suppression and selection of languages in unimodal bilinguals. Whether there is less need for subcortical, frontal parietal, and basal ganglia involvement in adjudicating the demand of two languages when they are expressed in decidedly different modalities is an active area of research (see Emmorey, Giezen, & Gollan, 2015, for a review of the psycholinguistic literature).

Recent fMRI studies have reported resting-state and task-dependent functional connectivity analyses of the dorsal anterior cingulate (dACC) and the left caudate nucleus (CN) in a small group of late Mandarin-CSL bimodal bilinguals (L1 spoken Mandarin, L2 Chinese Sign Language) (Li et al., 2015; Li et al., 2016). The modality of naming (speech or sign) modulated the functional connectivity of the dACC either to a predefined speech-based region in the left middle superior temporal gyrus (STG) or to a predefined sign language region in the left superior pre/postcentral gyrus (PCG). The increase in functional connectivity may reflect the control process of monitoring and promoting the activation level of the target language. Functional connectivity between the left CN and left PCG (the region for signed language) was similar when producing either CSL or Mandarin within a single-language context. The left CN was more connected with the left STG (the region for spoken language) when producing CSL than when producing Mandarin. This asymmetry may reflect an inherent dependency of L2 (CSL) on L1 (Mandarin) in this population and the left CN's greater role in controlling the less proficient language (Tan et al., 2011; Zou et al., 2012). These initial studies suggest that despite differences in modality, cognitive control mechanisms are engaged during single-language and dual-language tasks in ways that appear similar to language control in spoken-language bilinguals.

Reading

Studies investigating the processing of written language in deaf populations are of interest for two reasons. First, as noted earlier, the L2 of many signers, both native and late learners, is a written form of a language such as English. This is itself a unique situation in terms of bilingual language processing and linguistic representation. Second, many deaf individuals do not reach a high level of reading competency, despite years of instruction and educational interventions. Studying orthographic processing in deaf individuals can illuminate the relationship between cognitive organization and reading proficiency.

Data from deaf bilinguals have contrasted patterns of activation for sign language and written language. Neville and colleagues (1998) examined responses in deaf and hearing native signers, and a control group of hearing monolinguals, while participants read English sentences. The hearing native signers' activation during English sentence reading was a subset of activation seen in the monolingual hearing control group and included prominent frontal lobe activation, including the dorsolateral prefrontal cortex (DLPC) and Broca's area, posterior STS, and posterior parietal regions including angular gyrus. This activity was strongly left-lateralized and showed that regions active during English reading were also active while observing ASL signing. In contrast, deaf native signers' responses to written English were quite variable and statistically much weaker. While left frontal regions, including the DLPC, Broca's area, and precentral sulcus, were activated during reading, superior temporal sulcus activation was limited to middle and posterior regions, with the greatest activity seen in the right hemisphere, a pattern that contrasts with both monolingual controls and hearing native signers. Activation in posterior parietal regions, including IPS, anterior occipital sulcus, and angular gyrus, were largely bilateral and more strongly right-lateralized in the deaf participants; these patterns were not observed in either of the hearing groups.

Subsequent work has indicated that patterns of activation for L2 reading in ASL signing deaf participants may vary as a function of proficiency. Corina et al. (2013) examined neural activation during implicit word reading. Proficient deaf readers activated left inferior frontal gyrus and left middle and superior temporal gyrus in a pattern that is consistent with regions reported in hearing readers. In contrast, the less-proficient readers exhibited a pattern of responses characterized by inferior and middle frontal lobe activation that was stronger on the right hemisphere. This bears some similarity to areas reported in studies of logographic reading, raising the possibility that these individuals are using a qualitatively different mode of orthographic processing than is traditionally observed in hearing individuals reading sound-based scripts. The variability may also point to differences in age of acquisition/mastery, and differential reliance upon declarative memory systems.

Cross-modal Plasticity

Studies have routinely reported activation of the temporal lobes in response to signing. Petitto et al. (2000), and Nishimura et al. (1999) reported significant activation in the left superior temporal cortex, a region often associated with auditory processing, in response to the perception of single signs. MacSweeney et al. (2002b) also observed the activation of auditory association areas in deaf and hearing native signers of BSL. Their findings revealed relatively greater activation for deaf native signers than hearing native signers in the left temporal auditory association cortex during the perception of signed sentences (see also Kassubek, Hickok, Erhard, & 2004). These findings are taken as evidence of cross-modal plasticity whereby auditory cortex and auditory association cortex may be modified in the absence of auditory input to become specialized for visual language input. While this left hemisphere auditory activation is presumed to reflect linguistic processing, the functional significance of these activations is not well understood. Cardin et al. (2013) has presented data that suggest that right superior temporal lobe activation reflects cross-modal plasticity related to auditory deprivation.

A small number of morphometric studies that examine the presence of anatomical differences in the brains of deaf and hearing participants have provided further evidence for cross-modal plasticity. Two studies have reported reduced white matter in the left posterior superior temporal gyrus in deaf subjects, but no difference in gray matter volume in temporal auditory and speech areas (Emmorey, Allen, Bruss, Schenker, & Damasio, 2003; Shibata, 2007). It is speculated that the reduced white matter volume may indicate a hypoplasia in the development of specific tracts related to speech. The finding that auditory cortices show no differences in gray matter volume has been taken as evidence for preserved functionality of these regions, perhaps in the form of cross-modal plasticity.

SIGN LANGUAGE AND NEURODEGENERATIVE DISEASES

There is growing interest in the behavioral sequela of sign-language processing in the face of neurodegenerative diseases. These studies hold potential for understanding the contributions of specific neurotransmitter systems and synaptic molecular mechanism in the expression of sign language behaviors.

Parkinson's Disease

Parkinson's disease is a degenerative disorder of the brain that affects the extrapyramidal motor system and is mainly characterized by progressive tremor, bradykinesia (slowness of movement), and rigidity. Degeneration of the substantia nigra with subsequent decrease of striatial dopamine is responsible for the motor and cognitive disturbances seen in Parkinson's patients (Rodriguez-Oroz et al., 2009). The motor deficits observed in these subjects are not specific to language, but are evidenced across the general domain of motor behaviors (see Copland & Angwin, Chapter 33 in this volume).

Studies of deaf signers with Parkinson's disease highlight the importance of the extrapyramidal motor system and basal ganglia in the mediation of sign language. The sign-language deficits observed in Parkinsonian signing are an expression of the generalized motor impairments common in Parkinson's disease. Poizner and colleagues have presented several case studies of Parkinsonian signers (Brentari, Poizner, & Kegl, 1995). Signers with Parkinson's disease have been described as signing in a monotonous fashion, with a severely restricted range of temporal rates and tension in signing, two features that normally serve to signal emphasis. Accompanying restrictions in limb movements are deficits in the motility of facial musculature, which further reduce expressivity in signing.

In Parkinsonian signing, the scope of sign movement and the precision of articulation are compromised. In Parkinsonian signers, physical contacts between the major articulators and body locations may be entirely lost. The lack of contact is consistent with a description of overall smoothing of articulation in signers with Parkinson's disease; maintenance of physical contacts with body locations probably places significant demands on the updating and programming of movement plans used in signing. There is often a systematic reduction of sign articulation as well, which results in signs being articulated at the torso (as opposed to distinct, lexically specified locations). For example, Brentari and Poizner (1994) report their subject R. H. as signing "boy," normally articulated on the forehead, at the torso level. In fact, most of R. H.'s signs were articulated near the waist during free conversation. The handshapes of signers with Parkinson's disease are often quite lax, and do not maintain the crisp closure or opening of finger postures seen in normal signing. Importantly, the handshapes observed (and indeed all the articulatory distinctions) are approximations of the intended form, and not incorrect substitutions (Brentari & Poizner, 1994). These findings are consistent with a general disruption of motor control that leads to phonetic disruptions in signing. This can be contrasted to the phonemic disruption apparent in aphasic signing.

Alzheimer's Disease

Recent studies of patients with suspected Alzheimer's disease reveal the relationship between memory deficits and sign language. A case study reported by Falchook and colleagues (2013) illustrates a patient with deficits in episodic and working memory that resulted in a tendency to produce short sentences, and deficits in sign comprehension, syntax, and pronouns, as well as sign fluency, sign repetition, and naming problems (anomia). A PET scan revealed hypometabolism bilaterally in the parietal and anterior temporal lobes (greater in the left hemisphere than right), consistent with a diagnosis of Alzheimer's dementia. Synaptic loss in the cortex is the major correlate of the patterns of cognitive decline in Alzheimer's disease.

While there was no evidence of semantic or formational paraphasias in this patient's signing, two specific deficits were particularly striking: impaired fingerspelling[2] comprehension and recall, and impaired sentence repetition. In deaf signers, fMRI studies of fingerspelling comprehension show activation of the visual word form area, which is more left-lateralized than signs, paralleling the difference between reading and listening for spoken language (Emmorey, McCullough, & Weisberg, 2015). The deficits in sentence repetition were, on the other hand, attributed to impairments in working memory for verbal and visual spatial abilities. This is consistent with neuroimaging studies of working memory processes in users of sign language, which also have reported modality-specific activations in response to the perception and maintenance of sign-based information. These activations typically include bilateral temporal-occipital activations and activations in the posterior parietal cortex (Buchsbaum et al., 2005; Pa, Wilson, Pickell, Bellugi, & Hickok, 2008; Rönnberg, Rudner, & Ingvar, 2004).

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[2] Fingerspellings used in signed languages are often considered ancillary systems that are used to borrow orthographic representations into a manual form. Fingerspelling in ASL requires complex sequences of handshapes that represent letters of the English alphabet.

Sign Language and Human Action Understanding

There is growing interest in the relationship between sign-language processing and human gesture understanding, fueled by mirror neuron-based accounts of language evolution and language processing (Arbib, 2005, 2008). Rizzolatti and Arbib (1998) propose that a human analog of the bilateral fronto-parietal macaque mirror neuron system that subserves action execution and action perception supports a variety of complex socio-cognitive phenomena, most notably human action understanding and human language. Signed languages provide an important opportunity to examine such hypotheses, as sign production requires the orchestration of complex manual gestural forms and its comprehension depends on the direct perception of these same gestures.

Some support for the involvement of a unified action perception/action execution system for sign language comes from consideration of the functional role of the parietal lobes in sign language behaviors. Mirror neuron system accounts of language processing hold that one and the same region should participate both in the production and comprehension of language forms. Corina and Knapp (2006) reviewed neuroimaging data from studies of sign-language production and sign-language comprehension and examined regions that showed significant overlap. One region that showed compelling overlap was in the left SMG of the inferior parietal lobe. Lesion studies have shown evidence for sign-comprehension deficits with damage to left inferior parietal regions, and both lesion and stimulation mapping studies have shown impairment in sign production implicating the SMG. This is a region that is often observed in studies of sign-language working memory (Buchsbaum et al., 2005; Pa et al., 2008; Rönnberg et al., 2004). In hearing individuals, this region is considered a polymodal association region, with involvement in tasks that include phonological short-term memory (Jacquemot & Scott, 2006), judgments of hand gestures (Hermsdorfer et al., 2001), motor attention to limb movements (Rushworth, Krams, & Passingham, 2001), and phonological agraphia (Alexander, Friedman, Loverso, & Fischer, 1992). Given this multiplicity of functions of the SMG, it is perhaps not surprising that aspects of sign comprehension and sign production are subserved by this region. Whether individual neurons within this region exhibit mirror properties remains an important question (see Chong, Cunnington, Williams, Kanwisher, & Mattingley, 2008, for example).

It must be noted, however, that data from lesion and neuroimaging studies also place some limits on the feasibility of the mirror neuron account of sign language. For example, researchers have suggested that Broca's region is a likely homologue of macaque F5, a frontal ventral region where neurons with mirroring properties have been observed (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Yet, as discussed, studies of aphasic patients show that damage to left frontal ventral and opercular regions do not result in comprehension deficits in signers, as would be predicted from a mirror neuron account of human language. Recent group-level analyses of signing aphasics reinforce this point (Rogalsky et al., 2013). In addition, case studies of deaf signers have shown compelling dissociations between nonlinguistic pantomime and sign-language abilities. Patient W. L., for example, produced and comprehended pantomime normally, but demonstrated marked deficits in sign-language production and comprehension (Corina, et al., 1992). His gestures were clearly intended to convey symbolic information that he ordinarily would have imparted with sign language. Marshall et al. (2004) report on the dissociation of sign and gesture in Charles, an aphasic user of BSL. His ability to use nonlinguistic gesture was intact, while sign language expression showed significant impairment.

These accounts are difficult to reconcile within a human mirror neuron system view of action execution and perception that fails to distinguish between different classes of human actions. Data from neuroimaging studies that have directly compared the perception of different classes of human actions and signs in deaf signers also show little evidence of overlap in the neural system mediating the perception of transitive and intransitive human actions, pantomimes, and linguistic signs (Corina et al., 2007; Emmorey, Xu, Gannon, Goldin-Meadow, & Braun, 2010). In these studies, sign-language forms activate the familiar perisylvian language areas, while nonlinguistic human actions and pantomimes show prominent activation in the inferior occipital-temporal regions in deaf signers. One explanation for these differences is that deaf signers may show a greater reliance on top-down processing in the recognition of signs, leading to more automatic and efficient early visual processing of highly familiar linguistic features. In contrast, nonlinguistic gesture detection may be driven by bottom-up processing, in which preliminary visual analysis is crucial to interpretation of these forms.

Conclusions

Patterns of deficits seen in deaf signers following left and right hemisphere lesions show great commonalities to the deficits seen in users of spoken languages. Functional imaging studies of sign-language comprehension and production in deaf and hearing signers provide further evidence for the uniformity in the neural systems underlying spoken and signed languages. Taken together, these studies provide evidence for a core neurobiological system that underlies human language, regardless of the modality of expression (Fedorenko, Behr, & Kanwisher, 2011). At the same time, studies of sign language have also revealed instances in which the properties of sign languages invoke neural- processing resources that differ from those observed for spoken languages. These instances illuminate the intimate connections between language modality and brain structures for language. Structural imaging studies of deaf signers have begun to observe and differentiate the roles of sensory and language experience in sculpting cortical connections, while neurolinguistics studies of signed languages have been used to both motivate and constrain models of language evolution and language biology. Studies of signed languages and the experiences of deaf individuals provide an important means to advance our understanding of the neurobiology of human language.

Acknowledgments

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CHAPTER 17

UNDERSTANDING HOW WE PRODUCE WRITTEN WORDS

Lessons from the Brain

BRENDA RAPP AND JEREMY PURCELL

The vast majority of our current understanding of how we produce written language has come from the behavioral study of neurologically intact individuals and individuals with neural impairments: psycholinguistic and cognitive neuropsychological investigations, respectively. More recently, however, neural evidence from both neuroimaging and lesion-based investigations has provided a source of valuable information not only regarding the neural bases of the cognitive processes involved in written language production, but also regarding the cognitive processes and representations themselves. This chapter will focus on the latter and will summarize and evaluate the contributions to our understanding of written word production that come from the study of the brain, highlighting the specific issues to which neural data have made particularly significant contributions.

The Cognitive Processes and Representations of Written Word Production: An Overview

A basic functional architecture of word spelling is depicted in Figure 17.1. The production of written words occurs in a variety of situations, based on different types of inputs to the writing system. For example, we write the words we hear when we take notes in a lecture, or write a phone message, or we write to express internally generated word meanings when composing letters, text messages, essays, and so on. The operations

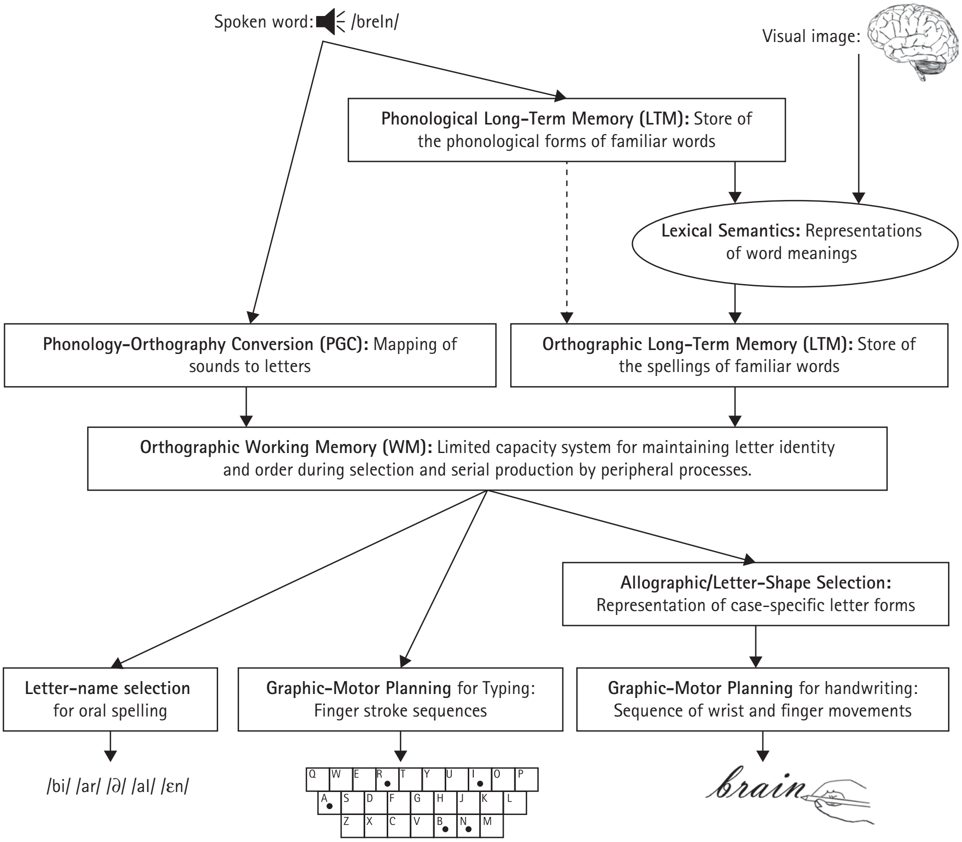
Spoken word: /breIn/
Visual image:
Phonological Long-Term Memory (LTM): Store of the phonological forms of familiar words
Lexical Semantics: Representations of word meanings
Phonology-Orthography Conversion (PGC): Mapping of sounds to letters
Orthographic Long-Term Memory (LTM): Store of the spellings of familiar words
Orthographic Working Memory (WM): Limited capacity system for maintaining letter identity and order during selection and serial production by peripheral processes.
Allographic/Letter-Shape Selection: Representation of case-specific letter forms
Letter-name selection for oral spelling
Graphic-Motor Planning for Typing: Finger stroke sequences
Graphic-Motor Planning for handwriting: Sequence of wrist and finger movements
/bi/ /ar/ /∂/ /aI/ /εn/
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
brain

FIGURE 17.1. The cognitive operations used in written word production. Note that the nonsemantic lexical route is indicated with dashed lines; components that are specifically involved in spelling are bolded.

involved in processing the different input forms and formats and contacting meaning representations are not specific to writing; rather, they are engaged whenever heard words or objects are processed or message representations are internally generated. Only once the system for word meaning representation (lexical semantics) is engaged can we retrieve stored knowledge of word spellings from *orthographic long-term memory* (O-LTM), also referred to as the orthographic lexicon (Buchwald & Rapp, 2009). In addition to the retrieval of spellings from O-LTM, spellings may also be generated through the application of knowledge regarding the relationships between sounds and letters via a process that is often referred to as *phonology-orthography conversion* (POC). This process generates plausible spellings for known words (“sauce” → SOSS) or for unfamiliar names or other novel words (“flove” → FLOAVE). Orthographic representations, whether retrieved from O-LTM or assembled through POC, are assumed to consist of, at a minimum, abstract letter identities and their order (D1+O2+G3) that are processed by an *orthographic working memory* (O-WM) system (often referred to as the graphemic buffer). Like other working memory systems (e.g., phonological working memory), O-WM is a complex system with multiple functions, including those required to keep orthographic information active and differentiated (Costa, Fischer-Baum, Capasso, Miceli, & Rapp, 2011) as well as processes needed for the serial selection of letters in their correct order for production by subsequent processes. O-LTM, O-WM, and POC are all involved in producing spellings, regardless of production format or motor effector: oral spelling (saying the names of letters), typing, producing letter shapes with the right or left hand, with a foot in the sand, a can of spray paint, and so on. For written spelling, letter shapes are selected via processes sometimes referred to as *allographic conversion* (specifying case and font) and then graphic motor plans are assembled and executed to produce specific letter forms (e.g., dOg). For oral spelling, letter names are selected from phonological long-term memory (i.e., the phonological lexicon) and the necessary phonological, phonetic, and articulatory processes are deployed to say the letter names (e.g., /di/ /oʊ/ /ʤi/).

Evidence for these component processes and for the connectivity structure among them (Figure 17.1) has come primarily from cognitive neuropsychological investigations of individuals with acquired dysgraphia (for recent reviews, see Miceli & Costa, 2014; Rapp & Fischer-Baum, 2015), although psycholinguistic studies with neurotypical individuals have increasingly constituted an important source of evidence (Bonin, Peereman, & Fayol 2001; Breining, Nozari, & Rapp, 2016; Damian & Bowers, 2003). Despite considerable consensus regarding the architecture depicted in Figure 17.1, numerous questions remain regarding even fundamental aspects. This chapter reviews some of these fundamental issues, highlighting the contribution of neural evidence to ongoing debates.

The Relationship Between Orthographic Long-Term and Working Memory

In the broader context of the literature on working memory, one persistent question has concerned the relationship between working memory (WM) and long-term memory (LTM) and specifically the extent to which these are distinct, independent systems (see Buchsbaum, Chapter 32 in this volume; see Miyake & Shah, 1999, for a review). There are theories that assume structural distinctions between the two, and others that assume that WM refers to the portion of LTM that is activated during task performance. For example, Cowan (1999, p. 62) proposed that "WM information comes from hierarchically arranged faculties comprising: (a) LTM; (b) the subset of LTM that is currently activated; and (c) the subset of activated memory that is the focus of attention and awareness" (see also Ruchkin, Grafman, Cameron, & Berndt, 2003). The "embedded processes" account stems from numerous findings indicating that different aspects of LTM knowledge and skills have effects on WM tasks and capacity. These findings have, in fact, led most researchers to acknowledge that the two systems cannot be entirely independent. On the other hand, various empirical findings, including neuropsychological ones, have supported independent systems accounts. This position is well-represented by Baddeley and Logie's (1999, p. 31) statement that "although some have viewed working memory as an activated portion of LTM, such a view is probably an unhelpful oversimplification." It would seem that a plausible hybrid account is that the two are structurally independent systems that, nonetheless, interact during processing. For a hybrid account, key questions concern the extent, nature, and conditions of the interaction.

While work on LTM and WM distinctions has most commonly occurred in the context of tasks that involve the presentation of sensory information (e.g., lists of visually or auditorily presented letters, words, shapes, spatial locations) for short-term retention and processing, there is also work that specifically involves the retrieval of information from LTM for processing by WM (Roth & Courtney, 2007). In fact, as described earlier, this is precisely the context in which the LTM and WM distinction applies in written word production. As reviewed previously, theories of written word production posit a distinction between an orthographic long-term memory store of known word spellings (O-LTM) and a limited-capacity orthographic working memory system (O-WM) that maintains active information about letter identities and their order and allows for the serial selection of the letter identities in their proper order for production by downstream processes. This distinction was motivated by the computational demands of word spelling (Caramazza, Miceli, Villa, & Romani, 1987) and supported by cognitive neuropsychological findings. In terms of computational demands, Caramazza et al. (1987) argued that O-WM (graphemic buffering) is required to interface between O-LTM processes that retrieve whole-word spelling representations (consisting of multiple letters) and subsequent processes involved in producing the individual letters sequentially.

Supporting this distinction, cognitive neuropsychological findings have revealed two highly distinct patterns of acquired dysgraphia (for a review, see Buchwald & Rapp, 2009). The pattern attributed to O-LTM impairment is characterized by higher error rates for low- compared to high-frequency words. This is attributed to differences in the robustness of LTM representations due to frequency of use, with the effect that more robust representations are less susceptible to disruption under conditions of brain damage. Furthermore, in these deficits accuracy is not affected by the length of words, with errors occurring equally often for longer words and shorter words. In these cases, errors are typically (although not necessarily) "word-level" errors and may include other words, semantic errors, or phonologically plausible spellings. In contrast to this pattern, the characteristics of O-WM impairments are thought to be the consequence of disruption and further limitations on the capacity-limited O-WM system. In fact, a deficit in O-WM is characterized by a largely complementary pattern in which there are no (or only mild) effects of word frequency, and there are effects of word length such that there is a greater probability of error on any given letter, depending on the total number of letters in a word. Errors in cases of O-WM deficits are typically "letter-level" errors consisting of letter deletions, substitutions, transpositions, or additions. The pattern observed for O-WM deficits corresponds to what is generally expected in situations where WM processes are damaged or taxed.

While the reported patterns of impairment appear quite distinct, Sage and Ellis (2004) questioned the true distinctiveness of the patterns and, therefore, the independence of the O- LTM and O-WM (see also Glasspool, Shallice, & Cipolotti, 2006; Ward & Romani, 1998). Furthermore, a computational model of spelling—Competitive Queueing (Houghton, Glasspool, & Shallice, 1994)—does not clearly differentiate these components. Buchwald and Rapp (2009) responded to these concerns by laying out a number of arguments in favor of the robustness of the differences between the two patterns while, at the same time, allowing for some interaction between the O-LTM and O-WM components. Recently, Rapp, Purcell, Hillis, Capasso, and Miceli (2016) reported neural findings highly relevant to understanding the nature and extent of the distinction between O-LTM and O-WM. This study was based on the analysis of lesion loci of 33 individuals with acquired dysgraphia: 17 with O-LTM impairment, 10 with O-WM impairment, and 6 with both (O-Mixed). Individuals were identified for the study based only on their behavioral profiles, with no consideration of lesion loci. A voxel-based lesion mapping analysis was then carried out in order to determine if there were voxels specifically associated with O-LTM or O-WM impairments. The results of the analysis are depicted in Figure 17.2, revealing (1) a distinct neurotopographic distribution of lesions producing O-LTM and O-WM deficits; (2) that lesions selectively associated

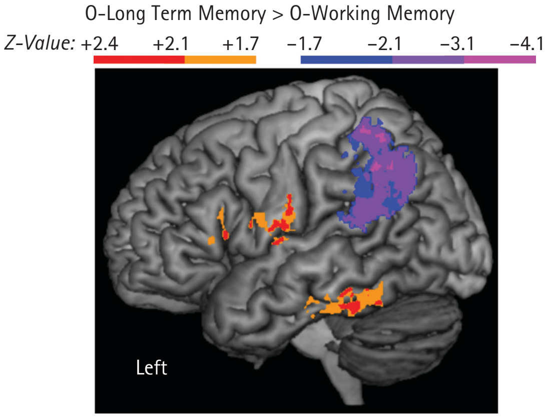
O-Long Term Memory > O-Working Memory
Z-Value: +2.4 +2.1 +1.7 −1.7 −2.1 −3.1 −4.1
Left

FIGURE 17.2. Voxel-based lesion mapping comparison of the lesions of individuals with orthographic long-term memory (O-LTM) and working memory (O-WM) deficits, Depicted are the results of testing (at each voxel) for differences in presence/absence of lesion for individuals with deficits affecting O-LTM or O-WM. Clusters of significant difference are rendered on a left hemisphere standard brain template. All clusters are FDR (false discovery rate) corrected for multiple comparisons at a $p < 0.05$. The color scale reflects the range z-values for the significant clusters. Positive z-values (orange/red) indicate the O-LTM deficit clusters; negative z-values (blue/purple/pink) indicate O-WM deficit clusters.

Source: Rapp et al. (2016).

with O-WM impairments occurred in the left superior parietal lobe (centered on the intra-parietal sulcus, −39, −50, 36); and (3) a fractionation of O-LTM into a left ventral temporal and a posterior inferior frontal gyrus (IFG) site, with lesion densities centered on −49, −39, −19 and −52, −19, 18, respectively. These findings advance our understanding of the spelling process in three ways.

First, the highly distinct neurotopographic distribution of the lesions provides strong support for the notion of structurally distinct O-LTM and O-WM processes. In this regard, it is also worth noting that none of the lesions in the seven O-LTM cases with ventral temporal damage extended outside the temporal lobe. Likewise, the lesions for the 10 O-WM cases did not extend into ventral temporal cortex. In other words, these subsets of O-LTM and O-WM cases had *non-overlapping* lesions. While these findings do not, of course, reveal the nature and extent of the processing interaction between the components, they do reveal that distinct and quite distant brain regions subserve these computationally "close" processes. The lesion locations identified in Rapp et al. (2016) are consistent with previous lesion studies linking O-LTM deficits with lesions to the left ventral temporal region (Rapcsak & Beeson, 2004) as well as the left posterior IFG (Hillis et al., 2002). Importantly, the locations identified with O-LTM and O-WM lesions are also highly convergent with previous fMRI findings with neurotypical adults. In an fMRI study during which participants carried out written spelling while being scanned, Rapp and Dufor (2011) identified specific regions that were associated with sensitivity to word length but not frequency (O-WM), as well as others associated with the complementary pattern of sensitivity to frequency but not length (O-LTM). The key activation sites identified by Rapp and Dufor (2011; see also Rapp & Lipka, 2011) included frontal and ventral temporal sites associated with O-LTM, as well as a parietal site associated with O-WM. In fact, the areas identified by Rapp and Dufor (2011) were in close proximity to the centers of high-density lesion overlap depicted in Figure 17.2.

Second, the parietal area associated with O-WM lesions has often been associated with spatial and/or visual WM/attentional processes (Jonides et al., 1998; Wager & Smith, 2003; Todd & Marois, 2004), although it is worth noting that these processes have been more consistently associated with the homologous area in the right hemisphere. Also associated with this parietal region are mechanisms supporting attention switching in visual (Serences & Yantis, 2006) and auditory (Shomstein & Yantis, 2006) displays, as well as more abstractly in the context of moving attention from one task to another (Shomstein & Yantis, 2004). In fact, the superior parietal locus of O-WM deficits raises questions regarding the domain specificity versus generality of the working memory processes subserved by this region. One possibility is that there are domain-specific WM processes that occupy adjacent parietal subregions with orthographic WM corresponding to a distinctly orthographic WM process; another is that this region supports domain-general WM processes. Favoring the orthography-specific hypothesis is the additional finding by Rapp et al. (2016) that the individuals with O-WM deficits performed within the normal range on visuospatial working memory, with spatial spans on the Corsi blocks task (Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000) averaging 4.75 (range = 4–5). This is a strong indication that visuospatial

WM was not generally disrupted by the (left hemisphere) lesions in these cases. Also favoring the possibility of orthography-specific WM processes in the left superior parietal lobule are functional neuroimaging findings of letter position WM processing for visually presented letters in this area (Carreiras, Armstrong, Perea, & Frost, 2014; Cohen, Dehaene, Vinckier, Jobert, & Montavont, 2008).

A third key finding form Rapp et al. (2016) was the fractionation of O-LTM into frontal and ventral temporal sites. This finding was somewhat unexpected given that the participants presented with the same overall behavioral profile of O-LTM deficits. One possibility is that the IFG and ventral temporal areas *together* instantiate a single, distributed O-LTM function. Another possibility is that the theory depicted in Figure 17.1 is underspecified with regard to its characterization of O-LTM processes and that, in fact, there are two distinct functions that both contribute to O-LTM, each supported by these different brain areas. Along these lines, Rapp et al. (2016) speculated that the frontal site may be involved in cognitive control for lexical orthographic selection, while the ventral temporal region may support the representation and storage of orthographic word forms. Consistent with this role for the ventral temporal site is the fact that this area (mid-fusiform gyrus, specifically) has been associated with orthographic lexical representation in reading (Cohen et al., 2002; Glezer, Jiang, & Riesenhuber, 2009), a topic we discuss in a later section.

In sum, the neural data—lesion and neuroimaging results—reveal substantially independent O-WM and LTM mechanisms. However, the findings do not provide a specific characterization of the nature of the interaction between the systems and, in this regard, key questions remain. A fundamental question is the following: Does O-WM constitute a short-term storage structure/work-space with "copies" of orthographic representations, or does it, instead, consist of specialized attentional processes that provide "top-down" amplification of orthographic information in O-LTM (Rapcsak & Beeson, 2015) and the serially directed attention required for letter selection for production? One can expect that, in the future, neural data may contribute to furthering our understanding of issues such as these.

The Relationship between Lexical and Sublexical Processes

The distinction between lexical and sublexical processes has been vociferously debated with regard to reading, although there has been little discussion of the parallel issues in the context of spelling. Nonetheless, the same issues do also apply to spelling, and so we provide a brief review of the debate in reading as a backdrop for the discussion of spelling.

Coltheart and colleagues (1993) proposed multiple routes to reading, including both semantically and non-semantically mediated *lexical* routes for reading words, and a non-lexical route for pseudoword reading (Figure 17.1 depicts an "analogous" architecture for spelling). Seidenberg and McClelland (1989) proposed an alternative theoretical position, arguing that the distinction between lexical and sublexical processing is unnecessary and that, instead, all oral reading can take place within a single network that maps orthography to phonology. In effect, this proposal reduces the two non-semantic routes proposed by Coltheart and colleagues to a single, non-semantic route. Importantly, in their view, this network does not include explicit lexical orthographic representations. Instead, knowledge of the relationships between letters and sounds at all levels of granularity—from letters to words—is encoded in the connections between letter and sound representations. In sum, the debate concerns if, in addition to a semantically mediated lexical route for word reading, there is a single non-semantic, non-lexical process that maps letters to sounds for all written strings, including both exception words and pseudowords, or if, alternatively, distinct lexical and non-lexical routes are responsible for non-semantic reading of exception words and pseudowords, respectively (see Rapp, Folk, & Tainturier, 2001, for a review).

Key evidence in support of the lexical/sublexical distinction has been the behavioral double dissociation consisting of individuals with intact pseudoword reading in the face of poor reading of exception words, and vice versa (Coltheart, Curtis, Atkins, & Haller, 1993). However, both patterns of dissociation have been questioned by opponents of this distinction. On the one hand, Plaut, McClelland, Seidenberg, and Patterson (1996) have argued that the pattern of intact pseudoword reading in the context of severely impaired exception-word reading is extremely rare and dependent on premorbid individual differences across individuals. Given the rather vague nature of the relevant individual differences, this argument has been difficult to evaluate. A different type of argument has been made to challenge the complementary pattern of impaired pseudoword reading in the context of intact word reading. Specifically, the argument has been that these cases do not reflect damage to reading processes at all but, instead, arise from disruption to phonological processes (Harm & Seidenberg, 1999; Patterson & Lambon-Ralph, 1999). Proponents of this claim have pointed to the strong association in the literature between phonological deficits and pseudoword reading difficulties. On this basis, these researchers have questioned the existence of reading-specific sublexical processes. In response, proponents of sub-lexical reading processes have pointed to the several well-documented reports of individuals with significant pseudoword reading difficulties plus good reading in the face of *intact* phonological processes (for a review, see Caccappolo-van Vliet, Miozzo, & Stern, 2004). These cases constitute a clear and strong challenge for the view that pseudoword reading deficits are reducible to phonological impairments and, in so doing, provide support for the view of independent lexical and sublexical reading processes.

As indicated earlier, the same issues and questions apply to spelling: Is the spelling of words and pseudowords handled by the same or different processes? Are there orthography-specific processes used for pseudoword spelling? Given the goals of this chapter, we will specifically focus on the neural evidence—neuroimaging and lesion analyses—that are relevant to these questions.

The appeal of a single-process proposal for spelling (analogous to Seidenberg and McClelland's [1989] proposal for reading) lies in the fact that our knowledge of the relationship between sounds and letters is learned largely from our experience with spelling words. Given that we must account for our word-spelling abilities, placing knowledge of word and pseudoword spelling within the same network eliminates the need to posit a mechanism by which a separate process or network is learned for sublexical spelling. Despite this positive aspect of the proposal, an important challenge has been to account for the many reports of behavioral dissociations between word and nonword spelling performance (e.g., for a review, see Tainturier & Rapp, 2001). The behavioral dissociations are matched by neural ones as well, which we will focus on here.

As indicated in the previous section, the neural substrates associated with O-LTM lesions correspond to the left inferior ventral region and areas of the posterior left frontal cortex (Rapcsak & Beeson, 2004; Rapp et al., 2016). With regard to pseudoword spelling deficits, Henry, Beeson, Stark, and Rapcsak (2007) reported that a group of individuals with perisylvian lesions exhibited greater difficulty in spelling pseudowords than words. For this group, the area of greatest lesion overlap was within the IFG/frontal operculum, precentral gyrus and insula, and, to a lesser degree, the superior temporal gyrus (STG) and the supramarginal gyrus. Other reports of selective pseudoword spelling deficits have also implicated posterior perisylvian regions, including the left supramarginal gyrus (Roeltgen, Sevush, & Heilman, 1983; also Alexander, Fischer, & Friedman, 1992; Bub & Kertesz, 1982; Philipose et al., 2007) and the angular gyrus (Hillis et al., 2002; Sheldon, Malcolm, & Barton, 2008). Generally, consistent with these findings, Rapp et al. (2016) found that the individuals with the ventral temporal lesions and O-LTM deficits all had good pseudoword spelling (85%–98% accuracy). This indicates that key pseudoword spelling processes are unlikely to be situated within the ventral-temporal lesion region and points, instead, to some role for frontal and/or perisylvian areas in pseudoword spelling. Thus, in combination, the lesion findings point to clear differences in the neuroanatomical regions supporting word and pseudoword spelling.

With regard to neuroimaging data, as indicated earlier, the findings with regard to O-LTM are convergent with the lesion-based findings, providing evidence for the role of ventral temporal cortex and posterior IFG. Rapp and Lipka (2011) found these regions to be sensitive to word frequency during spelling, and Rapp and Dufor (2011) confirmed those results while also providing evidence that these areas are not sensitive to word length in spelling. However, with regard to POC processes, there has been scant functional neuroimaging research. Ludersdorfer, Kronbichler, and Wimmer (2015) reported on the most detailed examination of word and pseudoword spelling to date. As depicted in Figure 17.3, within the left IFG and ventral temporal cortex, Ludersdorfer and colleagues found a neurotopographic differentiation between word and pseudoword spelling such that word spelling produced greater activity than pseudoword spelling. The word spelling recruitment of ventral temporal cortex was associated with O-LTM processing, and the left IFG recruitment was attributed to resolving competition among multiple orthographic representations that become active when spelling a word. Importantly, the only area in which pseudoword spelling resulted in more activity than

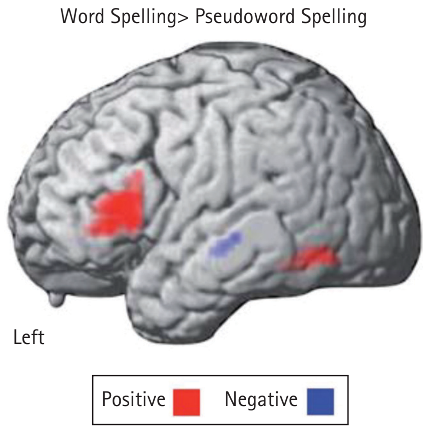

FIGURE 17.3. Areas selectively associated with word and pseudoword spelling. fMRI spelling experiment comparing neural response for word to pseudoword spelling. The red clusters in the left IFG and ventral occipitotemporal cortex (vOTC) depict areas with greater activity for word spelling than for pseudoword spelling. The blue cluster in the left STG depicts the area with greater activity for pseudoword than word spelling. Activation is projected onto a standard template brain in Montreal Neurological Institute (MNI) space.

Source: Adapted with permission from Figure 3 in Ludersdorfer et al. (2015).

word spelling was a region of posterior STG. This latter finding suggests that the STG region may be especially important for pseudoword but not necessarily for word spelling.

Overall, the functional neuroimaging and lesion mapping results point to a distinction between the roles of ventral temporal cortex for lexical processing and posterior perisylvian cortex for pseudoword processing. However, this does not identify which of the processes involved in pseudoword spelling are specifically supported by this region. At a minimum, these include the phonological processing of the input (e.g., segmentation), phonological working memory maintenance of the phonological input, or the phoneme-orthography correspondences themselves. With respect to POC, is this knowledge represented in a single region, or would it be encoded in the connection pattern between regions that otherwise represent phonemes and letters? In this context, the comparable recruitment of posterior ventral temporal cortex by both word and pseudoword spelling reported by Ludersdorfer et al. (2015) raises the possibility that single letter and multi-letter groups that are often assumed to be represented in this region are shared by both word and pseudoword spelling processes. However, on that basis, one would predict pseudoword spelling deficits with lesions in this region, but that has not been reported.

An intriguing aspect of the neuroimaging findings is the interpretation of the superior temporal/perisylvian findings provided by both Ludersdorfer et al. (2015) and Rapcsak et al. (2009). While both groups of researchers found an association of pseudoword spelling with either neural activity or lesions in this region, they both interpreted their findings as indicating that this region is specifically responsible for the phonological processing aspects of pseudoword spelling. For example, Rapcsak et al. (2009) reported that the degree of phonological impairment in their participants was predictive of spelling (and reading) accuracy and specifically concluded that pseudoword spelling difficulties (at least in cases of perisylvian lesions) are the result of a central phonological deficit, rather than damage to spelling knowledge per se. Along similar lines, Ludersdorfer et al. (2015) attributed the greater recruitment of STG by pseudoword compared to word spelling to the greater phonological demands of pseudoword spelling. Interestingly, these arguments parallel those we referred to in the context of reading (Patterson & Lambon-Ralph, 1999), according to which pseudoword deficits are reduced to phonological ones.

Although this is an area in which strong conclusions are premature, there are two things worth noting. First, while the interpretation offered by Ludersdorfer et al. (2015) and Rapcsak et al. (2009) is plausible, there is nothing in either the neuroimaging or lesion results that requires the interpretation that only phonological processing, rather than POC spelling processes, is associated with the STG/perisylvian sites. Second, these interpretations fail to provide an account of the neural (and cognitive) bases of pseudoword spelling. We certainly must have knowledge of the relationships between sounds and letters, which cannot be reduced to phonological processing since phonological processes alone cannot generate spelling responses. However, the "reductionist" phonological account of pseudoword spelling (or reading) and phonological dysgraphia leaves this fundamental question unanswered.

In sum, the differences in the neurotopography of brain regions active for word and pseudoword spelling support a distinction between lexical and non-lexical spelling processes that is independently motivated by the behavioral data from neuropsychological cases. Despite this, we still lack a detailed understanding of the distinctions between these processes and, in particular, we have little data regarding the neural instantiation of pseudoword spelling processes.

The Relationships between Reading and Writing

A key question in written language research is whether or not reading and spelling share representations and processes. These questions have been investigated in behavioral studies with neurologically intact adults and children, and with individuals with acquired deficits. The basic approach in much of this research has involved examining whether specific aspects of performance are highly similar or different in reading and spelling. Most of the research to date has focused on the possibility of shared O-LTM representations, with relatively little attention directed at the possibility of shared O-WM processes (but see Tainturier & Rapp, 2003) or at the relationship between letter recognition and production (but see Longcamp, Anton, Roth, & Velay, 2003; Rapp

& Caramazza, 1997). Consequently, here we will primarily focus on the question of whether or not spelling and reading share O-LTM, and then touch briefly on this issue as it concerns O-WM.

In behavioral studies with neurologically intact participants, Holmes and Carruthers (1998) and also Burt and Tate (2002) have shown that individuals are slower and/or less accurate in reading tasks (such as lexical decision or visual spelling accuracy judgments) for the specific words that they cannot spell correctly, providing support for the notion that O-LTM systems are shared for reading and spelling. Consistent with this, Monsell (1987) found significant repetition priming from the task of spelling (without visual feedback) to a subsequent reading task. While the behavioral evidence from neurotypical individuals would seem to generally favor shared O-LTM, arguments can be raised against this conclusion. For example, with regard to the more fine-grained patterns of behavioral associations/dissociations, the fact that the findings are largely correlational allows for the possibility that some additional factor is the source of the relationship across the modalities or, alternatively, that episodic memory traces from one task influence performance on the other.

In terms of acquired deficits, the straightforward prediction is that associations of reading and spelling deficits affecting lexical orthographic processing favor the view of shared O-LTM component(s), while dissociations of O-LTM deficits across reading and spelling would present a challenge to that view. While there have been a number of reports describing associations and dissociations between reading and spelling, for our purposes, the most relevant are those studies that determined whether or not O-LTM was specifically affected. As discussed earlier, Rapp et al. (2016) reported a number of cases with O-LTM deficits in spelling with lesions in ventral temporal fusiform cortex or posterior IFG. Interestingly, while many of those cases also had reading deficits, many did not; however, the reading deficits were not specifically evaluated in terms of whether or not they specifically affected O-LTM. However, Rapcsak and Beeson (2004) reported on eight individuals who suffered damage to left hemisphere Brodmann areas 37 and 20 and exhibited lexical impairments in both spelling and reading (though more pronounced in spelling) (see Philipose et al., 2007, for similar evidence from acute stroke). One of the challenges in interpreting the findings of associations and dissociations in acquired deficits is that associated acquired deficits could either signal a shared process or, alternatively, be explained as resulting from coincidental damage to independent O-LTM components for reading and spelling that are instantiated in adjacent neural substrates. Similarly, dissociations could indicate distinct O-LTM systems for word reading and spelling or result from lesions affecting modality-specific *access* to a single, shared O-LTM system (Allport & Funnell, 1981). In fact, Purcell, Shea, and Rapp (2014) used what they referred to as "cognitive dissociation lesion mapping" to examine the lesion distributions of three individuals: two with lexical deficits in both reading and spelling, and one with a lexical deficit in spelling but not reading. They suggested that there are separate substrates that support the interface between O-LTM and semantics for reading and spelling, respectively.

While one might have thought that it would be a relatively straightforward matter to determine if spelling and reading share processing mechanisms and representations, the number of alternative interpretations for existing deficit/lesion findings leaves open the possibility for functional neuroimaging data to make a significant contribution to the debate. There have been a large number of studies evaluating the neural substrates of reading, and a much smaller number that have considered spelling substrates (for meta-analyses of functional neuroimaging studies of reading, see Jobard, Crivello, & Tzourio-Mazoyer, 2003; Martin, Schurz, Kronbichler, & Richlan, 2015; and Turkeltaub, Eden, Jones, & Zeffiro, 2002; for spelling meta-analyses, see Planton, Jucla, Roux, & Démonet, 2013; Purcell, Napoliello, & Eden, 2011). However, there have been only a handful of studies that have examined both reading and spelling in the same individuals, something that is critical for addressing this issue via functional neuroimaging (Purcell et al., 2011; Purcell, Jiang, & Eden 2017; Rapp & Dufor, 2011; Rapp & Lipka, 2011) and these studies reported co-activation for reading and spelling in the left mid-fusiform gyrus and in left IFG/junction. Furthermore, both Rapp and Lipka (2011) and Rapp and Dufor (2011) found sensitivity to lexical frequency in these two regions. This latter finding strengthens the argument that the shared substrates between reading and spelling were specifically involved in lexical (orthographic) processing.

However, all of these studies except Purcell et al. (2017) relied on identifying overlapping areas of activation for reading and spelling. This leaves open the possibility that different O-LTM processes and/or representations for reading and spelling could be supported by different subpopulations of neurons within these overlapping regions. The neural adaptation approach taken by Purcell et al. (2017) is particularly well-suited for evaluating this possibility. Neural adaptation allows one to examine whether different cognitive functions (or representational types) share neural substrates. It is based on the finding that when a neural population is repeatedly engaged, its response diminishes. To determine whether the same neural population processes different tasks or stimulus types, one can compare the response of the area to the repetition of the same tasks/stimuli versus its response to the consecutive processing of the relevant different tasks/stimuli. If the same neural substrates support the different tasks/stimuli, then similar decreases in neural responses are expected in both situations. The finding of neural adaptation across different tasks/stimuli supports the conclusion that the brain area supports a cognitive function or representational type that is shared by the tasks/stimuli. Although fMRI-adaptation is a commonly used method to index the selectivity of a brain region to a task/stimulus representation (Barron, Garvert, & Behrens, 2016), these experiments require careful design, as the adaptation effect can be influenced by neural adaptation due to representational selectivity as well as by attentional expectation (e.g., heightened attention when a stimulus/task is different as compared to same) (Larsson & Smith, 2012; Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008). Therefore, fMRI-adaptation designs should compare conditions for which task/stimulus attentional expectations are equated. Purcell et al. (2017) used an fMRI-adaptation method of this sort to test the hypothesis that reading and spelling share orthographic representations. On different trials, participants were asked to read, spell, and repeat words. There were two critical conditions defined by the pairings of consecutive trial types: (1) participants spelled and then read the same or different words (i.e., spell-READ); (2) participants verbally repeated and then read the same or different words (i.e., repeat-READ). If, within a neural region, the same functions/representations support both reading and spelling, then we expect a benefit for consecutive processing of the same word (compared to different words) for the spell-READ condition. On the other hand, if the neural region does not involve functions/representations shared by both reading and spelling, then no more neural adaptation would be expected from this region for same compared to different words across the two tasks. The repeat-Read condition serves to establish whether any observed neural adaptation is specific to orthographic processing or is due, instead, to shared non-orthographic processes (e.g., phonologic or semantic). Figure 17.4 A depicts the lateral ventral mid-fusiform region, referred to as the VWFA (visual word form area; Cohen et al., 2002), that was functionally defined in each participant in the study; these individually defined regions served as the analysis region. Figures 17.4 B and C show the neural responses associated with each of the experimental conditions. These data clearly indicate a neural adaptation response when the same (vs. different) word is spelled and then read (spell-READ) but, critically, not when it is repeated and then read (repeat-READ); these conditions are equated on attentional expectation (i.e., the relative expectation of performing a same or different word READ task is equated across both the critical spell-READ and the repeat-READ condition pairs). These findings provide strong evidence that spelling and reading share *orthographic-specific* representations/processes within this brain region. The results are stronger than the previously described overlap results, as they constitute a stronger test that the same neural populations are involved in both reading and spelling.

Finally, we briefly consider the relationship between spelling and reading with regard to O-WM. In terms of the role of O-WM in spelling and reading, the few behavioral studies of acquired impairments that have examined the issue concluded that there is a shared O-WM (Caramazza, Capasso, & Miceli, 1996; Hillis & Caramazza, 1995; Tainturier & Rapp, 2003). In these papers, it was argued that in the case of spelling, words and pseudowords place roughly comparable demands on the O-WM system. In contrast, in reading, words place minimal demands on the system due to the fact that they are largely read in parallel, while pseudowords are considerably more taxing of O-WM (see Ans, Carbonnel, & Valdois, 1998 for similar arguments with regard to reading). Although the neural data are scant, they provide some contributions to this question. As reported earlier and depicted in Figure 17.2, Rapp et al. (2016) found that O-WM deficits in spelling can arise from lesions to the left superior parietal lobule and that this region has been associated with sensitivity to word length in neuroimaging studies of spelling (Rapp & Dufor, 2011). Interestingly, this general neural area has also been associated with reading under attentionally demanding conditions (Carreiras, Quiñones, Hernández-Cabrera, & Duñabeitia, 2015; Cohen, Dehaene, Vinckier, Jobert, & Montavont, 2008), leading to the suggestion that the O-WM area may provide "top-down," serially directed attention for letter selection in O-LTM regions during reading. While in reading this may be required only under demanding viewing conditions or specific tasks, this type of O-WM memory involvement may be routinely required for spelling.

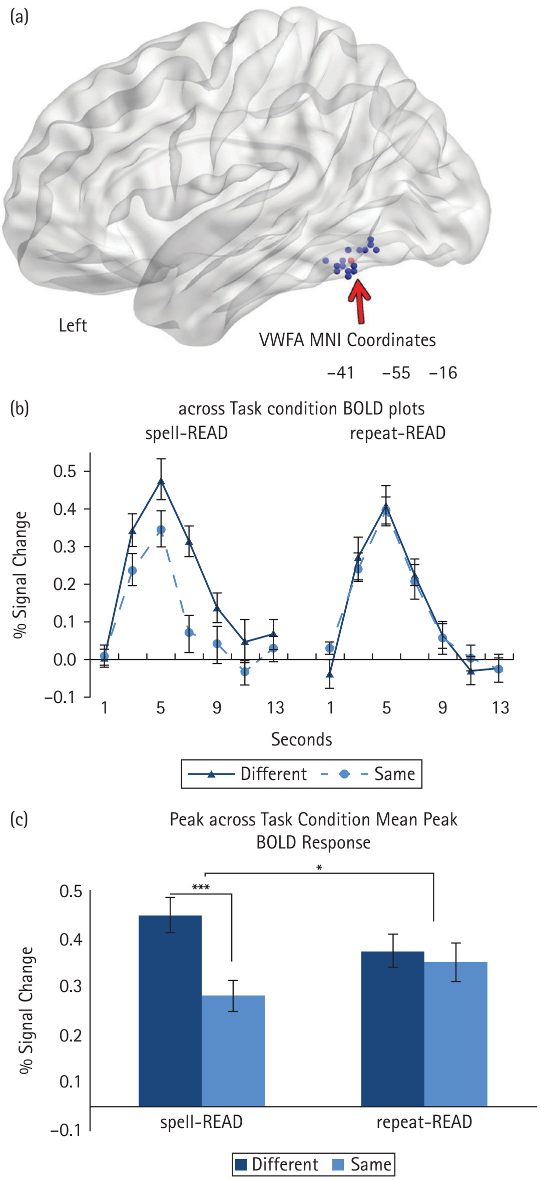

FIGURE 17.4. Neural adaptation in the left visual word form area (VWFA) region of interest, demonstrating orthographic representations/processes shared across spelling and reading. (A) The mean location of the participant specific VWFA regions projected onto a transparent left hemisphere standard brain. Red dot refers to the mean location across subjects (−41, −55, −16); the blue dots refer to the individual subject peak locations. (B) Blood oxygenation level dependent (BOLD) responses for the (spell-READ) and the repeat-READ consecutive task pairs of either different words (solid lines) or the same words (dotted lines). Error bars are standard error. (C) Average peak BOLD response (4–8 sec post-stimulus) differences for each condition. Positive values refer to an adaptation effect (i.e., different > same). Error bars are standard error. These results indicate a significant effect for the spell-READ conditions, but critically not for the repeat-READ condition, indicating shared orthographic representations *across* spelling and reading within the left VWFA.

P-values: *** $p < 0.0001$; * $p < 0.01$.

Source: Adapted with permission from Figure 4 in Purcell, Jiang, & Eden (2017).

In summary, the current neural evidence supports the hypothesis of shared lexical and working-memory processes in reading and spelling. However, much work remains to be done to determine the specific nature of the shared functions and representations; the possibility of dissociations in the access to and from these shared structures has been scarcely addressed and may require different methodological approaches.

Abstract Letter Representations in Writing

This section concerns the role of abstract letter identities (ALIs) in spelling. It is commonly assumed that the letter representations in O-LTM and O-WM are abstract or amodal representations that do not correspond to letter names or shapes. In the context of the architecture depicted in Figure 17.1, the ALIs retrieved from O-LTM or computed from POC are held in O-WM while serially converted to specific letters shapes or names, depending on whether the spelling knowledge is to be expressed in written or oral spelling. An alternative view would be that spelling involves a "re-instatement" of previous motor or perceptual experiences during writing, and therefore that letter representations used for spelling are *necessarily* motor (or visual) representations. Such a view would be consistent with the general embodied cognition framework (Barsalou, 2008; Pulvermüller, 2005).

The primary argument for ALIs in spelling is based on a combination of findings from cases of acquired dysgraphia. First, individuals with deficits affecting the central processes of spelling (O-LTM, POC, or O-WM) typically exhibit highly similar patterns of accuracy and distribution of error types across output modalities—written and oral spelling or typing (Caramazza & Miceli, 1990; see Tainturier & Rapp, 2001, for a review). This indicates that a common representational type forms the basis of written and oral spelling. However, it does not necessarily imply ALIs, as the common format could be motor plans, visual shapes, or letter names. However, if spellings were represented in a specific modality, then we would expect that disruption to representations in the critical modality would create a deficit in other modalities. However, this has not been the case. There have been reports of individuals with impaired oral spelling and intact written spelling (e.g., Bub & Kertesz, 1982; Kinsbourne & Warrington, 1965) where the oral spelling impairment did not involve apraxia or peripheral impairments. In a complementary manner, there have been a number of cases of individuals with intact oral spelling but impaired written spelling with no generalized motor deficits (among them, Rothi & Heilman, 1981; Zangwill, 1954). This double dissociation of written and oral spelling deficits argues against the position that either letter names or letter shapes correspond to the format of letter representation at the level of the central components of spelling and therefore is consistent with the ALI proposal. More direct evidence in favor of ALIs comes from Rapp and Caramazza (1997) who examined the letter substitution errors of individuals with deficits arising from O-WM deficits to determine if targets and error letters were similar either visually or motorically. They found that there was no more visual or motor similarity between target letters and errors than would be expected by chance, precisely what would be predicted under the view that orthographic knowledge is represented in the abstract, amodal format of ALIs, and contrary to the assumptions of an embodied account.

Neural data have also provided evidence relevant to this debate. Dufor and Rapp (2013) used the fMRI adaptation paradigm described above to examine the various representations of letters in writing, including ALIs. The logic was as follows: As depicted in Figure 17.5A, on each trial, participants were prompted to write three repetitions of a particular letter. This was expected to produce increasingly smaller BOLD responses (adaptation/habituation effects) in brain areas involved in letter production (see Figure 17.5B). On the fourth trial, either the same letter (no-change trial) or a different letter (change trial) was produced. Change trials could involve a change in case only (sssS), a change in case and shape (qqqQ), a change in identity and shape (tttp), or a change in identity, case, and shape (tttP). Comparisons of the magnitude of the BOLD response across the different types of change trials should reflect the extent of neural habituation or release from inhibition that has occurred, revealing the type(s) of representations processed in a given brain region. Areas that encode letter shape should respond to changes in shape, and areas that encode letter case should respond to changes in case regardless of changes in shape. Moreover, specifically as concerns ALIs, neural areas representing ALIs should show a release from adaptation when letter identity changes (tttP or tttp), but critically not when the letter identity remains the same, despite changes in case and size (e.g., vvvV) or case and shape (qqqQ).

Dufor and Rapp (2013) found that within letter-sensitive cortex, there were multiple regions that responded to changes in letter shape, and some that responded to both shape and identity, but none that responded only to changes in case. In addition, and critically relevant to the ALI hypothesis, there was one region—the left fusiform gyrus (centered on −41, −60, −13)—that showed the pattern expected of a region encoding ALIs: it responded to changes in letter identity more so than to changes in size, case, or shape only (e.g., tttP/tttp trials compared to vvvV/qqqQ trials); see Figure 17.5 C.[1] The implications of these findings are twofold. First, they provide positive evidence of ALIs in letter writing that demonstrates convergence with the cognitive neuropsychological evidence described earlier. Second, the specific neural location of the results is also informative. The neural responses consistent with ALIs were identified within the left fusiform region that—as we have seen throughout this chapter—has been independently associated with lexical orthographic representations in spelling (and reading) in neuroimaging with neurologically intact individuals and in lesion-deficit correlation studies. This association specifically strengthens the argument that the O-LTM orthographic representations that form the basis for spelling consist of abstract, case-independent letter identities.

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[1] These ALI selective effects are unlikely to have been driven by task/stimulus expectation given that, although there were more change than no-change trials, the different types of change trials were equi-probable.

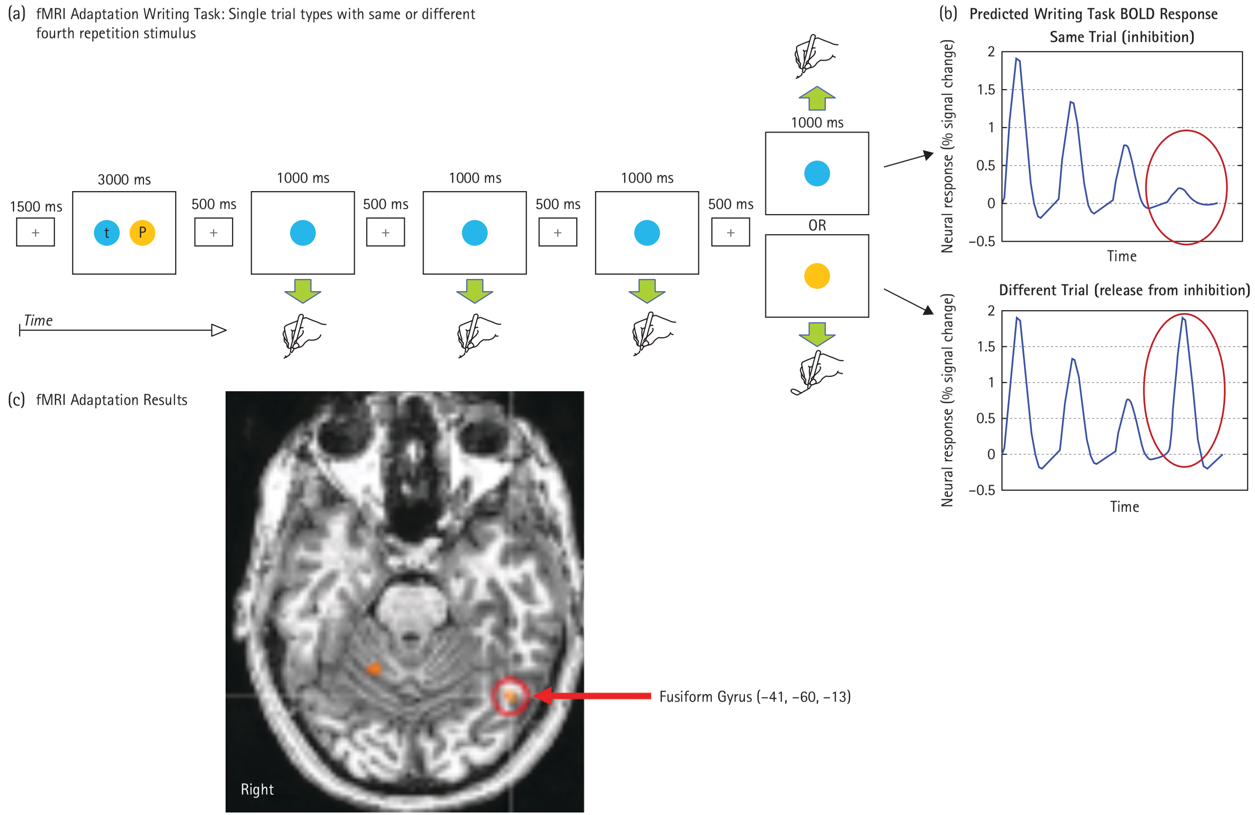
(a) fMRI Adaptation Writing Task: Single trial types with same or different fourth repetition stimulus
1500 ms
3000 ms
t
P
500 ms
1000 ms
500 ms
1000 ms
500 ms
1000 ms
500 ms
1000 ms
OR
Time
(b) Predicted Writing Task BOLD Response
Same Trial (inhibition)
Different Trial (release from inhibition)
Neural response (% signal change)
2
1.5
1
0.5
0
−0.5
Time
(c) fMRI Adaptation Results
Right
Fusiform Gyrus (−41, −60, −13)

FIGURE 17.5. Dufor and Rapp (2013) fMRI study of letter writing that provided evidence of abstract letter identities in spelling. (A) The sequence of events in a trial of the task used to measure neural adaptation: after associating two letters with two colors, each trial consisted of three repetitions of the same letter, followed by either a fourth repetition (same trials) or a different letter (change trials). Brain areas representing ALIs should show a release from adaptation when letter identity changes, but not when it does not, despite changes in size, case, or shape. (B) Predicted blood oxygenation level dependent (BOLD), depending on whether the trial's fourth stimulus was the same or different. What constitutes a change will be determined by the types of representations processed in a given brain area. (C) Within letter-sensitive cortical areas, only the left fusiform gyrus cluster (−41, −60, −13) exhibited greater release from inhibition for trials with identity changes (e.g., tttP or tttp) than for trials when the identity stayed the same but the case-size or case-shape changed (e.g., vvvV or qqqQ).

Source: Dufor & Rapp (2013).

LOOKING FORWARD

In this chapter, we have examined four fundamental issues of *cognitive* representation and processing in spelling: the distinction between orthographic long-term and working-memory, the distinction between lexical and sublexical spelling processes, the relationship between reading and spelling, and the role of abstract letter representations in spelling. For all of these issues, we have discussed neural findings that have contributed significantly to our understanding of these issues. In some cases, the neural data provided convergence with behavioral findings; in others, they provided unique contributions to the arguments. These detailed examples of the contributions of neural data to addressing cognitive questions is relevant to an ongoing debate between those who have argued that this is either not possible in principle (van Orden & Paap, 1997) or has not been achieved in practice (Coltheart, 2006) and those who have argued that neural data can be relevant to furthering our understanding of cognitive questions (Henson, 2006; see also de Zubicaray & Piai, Chapter 19 in this volume).

We have indicated many issues that remain unresolved, and many more important issues in written language production were not discussed. Few of these have received significant research attention, either behavioral or neural. Among others, these include similarities and differences in written production across different scripts and orthographic codes; spelling processes beyond the single word; and, importantly, the development and learning of spelling and writing (both normal development and developmental dysgraphia). In addition, there is a large variety of additional sources of neural data to be considered in addressing these issues. These include different forms of neural measurements and analysis with neurologicaly healthy individuals (e.g., ERP, MEG, resting-state fMRI, among others), as well as different etiologies of neural impairment. For example, in addition to investigations of deficits following stroke, trauma, or surgery, there are an increasing number of studies that involve the detailed study of the spelling deficits of individuals with progressive neurological disease (e.g., Graham, Patterson, & Hodges, 1997; Haslam, Kay, Tree, & Baronm, 2009; O'Dowd & Zubicaray, 2003; Primativo, Yong, Shakespeare, & Crutch, 2017). Clearly, therefore, there is much to be done and many contributions to come from neurolinguistics research on written language production. The approaches and techniques described here can be used to address some of these issues as well, but neuroimaging methods and analysis techniques are evolving rapidly, and will surely contribute to our ability to use these approaches to address increasingly detailed and sophisticated cognitive questions.

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CHAPTER 18

MOTOR SPEECH DISORDERS

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Introduction

Like any other motor system of the human body, the motor system involved in speaking can be impaired by lesions to the brain. As a consequence, the movements of the respiratory, laryngeal, and supra-laryngeal motor organs that contribute to the generation of speech are disordered, resulting in unnaturally sounding and/or unintelligible speech. Depending on which parts of the brain's speech motor network are affected, a diversity of syndromes may emerge, which are subsumed under the clinical terms *dysarthria* and *apraxia of speech* (e.g., Duffy, 2013). Patients with speech motor disorders represent the largest group among those suffering from neurogenic communication disorders, with an estimated prevalence of more than 4 per 1,000 in Germany. Dysarthria and apraxia of speech constitute a severe health problem because the afflicted persons may suffer from serious restrictions in their social and occupational participation (Schölderle, Staiger, Schumacher, & Ziegler, in press).

In the organization of this chapter, we use the functional neuroanatomy of motor speech as a framework to describe how speech motor control can be compromised by brain lesions, with a particular focus on some of the most controversial issues. In our interpretation of the available clinical data we will emphasize, in a final section, how deeply the motor system of speaking is entrenched in language and communication.

The Neural Basis of Speech Motor Disorders

Gross Architecture

Figure 18.1 gives a simplified overview of the gross architecture of the speech motor system (for a more detailed description, see Tremblay, Deschamps, & Dick, Chapter 15 in this volume). A core component is the primary motor cortex, located on the precentral gyri of both hemispheres, with its descending pathway to the cranial (and also several spinal) motor nuclei innervating the respiratory, laryngeal, and vocal tract muscles. Along this pathway, the motor commands originating in the motor cortical areas representing the speech muscles are conveyed to the speech organs (discussed later in this chapter). This descending pathway is supported by two loop systems through which the motor cortical information is continuously updated: the cerebellar loop and the basal ganglia ("striatal") loop (both discussed later in further detail). Together, these components—the corticobulbar system with the striatal and cerebellar loops—may be referred to as the *speech motor execution system*.

The motor execution network receives motor planning information from anterior peri- and/or subsylvian cortical regions of the left hemisphere, in Figure 18.1 referred to as left posterior inferior frontal gyrus (pIFG; see later discussion). This cortical area is connected with higher auditory processing areas in the superior temporal gyrus (STG) and with areas in the inferior-parietal and the parieto-temporal region of the left hemisphere—a network known as the *auditory dorsal pathway*. This pathway has a crucial role in higher order sensorimotor integration processes for speech, especially also as

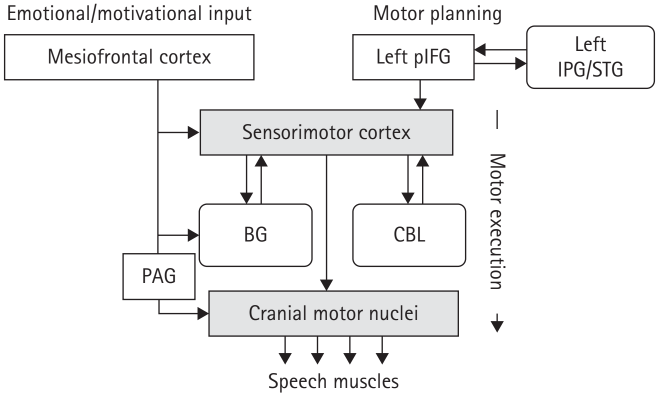

FIGURE 18.1. Simplified outline of the neural architecture of speech motor control.

BG: Basal ganglia; CBL: cerebellum; IPG: inferior parietal gyrus; PAG: Peri-aqueductal grey; pIFG: posterior inferior frontal gyrus; STG: superior temporal gyrus. Rectangles with rounded corners represent feedforward-feedback loop systems.

a relay system interfacing auditory with motor information (see, in this volume, Hickok, Chapter 20, and Poeppel, Cogan, Davidesco, & Flinker, Chapter 26).

Finally, the speech motor network also receives input from the anterior cingulate cortex (ACC) located at the medial walls of the frontal lobes, which is supposed to channel emotional and motivational input into the human motor control system for speaking.

This architecture will in the following serve as a guideline to describe the sequelae of brain lesions to speech motor control. For reasons of conciseness, the disturbances resulting from dysfunctions of the mesio-frontal ("limbic") motor network, including the supplementary motor area (SMA), will not be described in a separate section (for details on this issue, readers are referred to Ackermann, Hage, and Ziegler, 2014). Moreover, we will concentrate on the central nervous system and spare the dysarthric impairments resulting from lesions to the peripheral, lower motor neuron level of the speech motor system. Furthermore, the ascending sensory pathways projecting from the solitary tract and spinal trigeminal nuclei via thalamic nuclei to somatosensory areas on the postcentral gyrus will not be considered (cf. Jürgens, 2002). For a more comprehensive presentation of clinical issues, see Duffy (2013).

The Upper Motor Neuron System and Paretic Dysarthria

Functional Topography

The speech muscles receive their neural commands via the motor nuclei in the brain stem and in parts of the spinal cord. These commands have their origin in the ventral pre-central cortex (Brodmann area 4) of the left and right hemispheres, from where they travel along the cortico-bulbar tracts to the trigeminal motor (V_{mo}), the facial (VII), the ambigual (X), and the hypoglossal nuclei (XII) of the brain stem, as well as to motor nuclei in cervical and thoracic segments of the spinal cord. The corticobulbar and corticospinal motor tracts are referred to as the upper motor neuron (UMN) system. From the motor nuclei, the nerve fibers innervating the individual speech muscles (the lower motor neuron, LMN) originate. The LMN system will not be considered further in this chapter.

Apart from the facial nucleus innervating the muscles of the lower face, the brain stem motor nuclei of either side receive fibers from both hemispheres, but with a predominant input from contralateral motor cortex. In humans, all brain stem motor nuclei, including the nucleus ambiguus, receive direct (i.e., monosynaptic) input from primary motor cortex. This distinguishes the human speech motor system from the (nonhuman) primate vocalization system, which lacks dense monosynaptic motor cortical projections to the ambigual nuclei innervating the laryngeal musculature. As a hypothesis, the monosynaptic differentiation of the human corticobulbar tracts during phylogenesis is associated with the refinement of the behavioral repertoire of the human larynx involved in speech and articulation (for references, see Ackermann et al., 2014).

The cranial motor nuclei also receive parallel cortical input via indirect fibers synapsing at various sites in the striatum and the brain stem. These connections are considered to mediate primarily the regulation of reflexes, posture, and tone, rather than the fine-tuning of voluntary movements (e.g., Strominger, Demarest, & Laemle, 2012).

As in the limb muscles, the UMN system for speech has a somatotopic organization, with selective representation sites of the lips, tongue, larynx, and respiratory organs in the sensori-motor cortices (Brown et al., 2009). However, on a finer-grained level, the motor cortical fields of the speech muscles are arranged in a more intricate manner, with distributed and overlapping representational maps of individual muscles, and representations of complex, macro-scale muscle synergies. Multi-electrode recordings of speech-related motor-cortical electrical activity in individuals who underwent surgical treatment of epileptic seizures revealed complex temporal activation patterns for syllables, reflecting a high specificity of the organization of motor representations in primary motor cortex for the phonetic patterning of speech, presumably as a result of speech motor learning during language acquisition (Bouchard, Mesgarani, Johnson, & Chang, 2013). This corresponds with findings relating to skilled motor actions of the hands, according to which the learning of a motor skill shapes the representational maps of the involved muscles in primary motor cortex through mechanisms of learning-based neural plasticity (e.g., Matsuzaka, Picard, & Strick, 2007). We will come back to this issue later in the chapter.

Clinical Aspects

Lesions to the motor cortical representation areas of the speech organs and/or the descending fibers along their way to the brain stem lead to paresis (muscle weakness) and a syndrome termed *paretic dysarthria*. All levels of the speech motor apparatus can be afflicted to various degrees: weakness of the expiratory muscles may lead to short breathing cycles, weakness of the laryngeal muscles to impaired voice quality and monotonous intonation, and paresis of the vocal tract muscles to slowed and imprecise articulation (Duffy, 2013). Due to the bilateral organization of the corticobulbar pathway, one-sided lesions usually cause only mild dysarthria that may disappear within several days or weeks (Urban et al., 2006).

Though the term *paretic dysarthria* suggests muscle weakness as the core mechanism underlying this impairment, existing clinical data are not conclusive regarding the complex pathophysiological conditions resulting from lesions to the UMN system supplying the speech muscles (upper motor neuron syndrome, UMNS). In the limb muscles, paresis in UMNS is mostly accompanied by "positive" signs in addition to weakness (i.e., muscular overactivity and spastic hypertonus; Sheean, 2002). Since hypertonus and muscular overactivity can also be visible in the speech musculature (e.g., hyperadduction of the vocal folds during laryngoscopy) and inferred from deviant speech parameters (e.g., strained-strangled voice), the term *spastic dysarthria* has become established. However, the patho-mechanisms underlying these signs are largely unknown—not least because the spinal reflex mechanisms underlying spasticity in the extremities cannot be transferred straightforwardly to the muscles implied in speaking.

Moreover, the methods to assess spasticity in the arms and legs are not applicable to the speech motor apparatus. It is hypothesized that spastic hypertonus in the speech muscles results from lesions of the indirect fibers traveling from motor cortex to the brain stem nuclei. Since the signs of spastic hyperactivity are usually absent in patients suffering from lesions to the lower motor neurons, the speech impairment resulting from LMN lesions is referred to as *flaccid dysarthria* (Duffy, 2013).

Apart from weakness, another negative sign of the UMNS is loss of dexterity, for example in hand and finger movements (Sheean, 2002). As is known from hand motor control, an important neural basis of functional dexterity must be sought in (1) the task-specific organization of representational maps in primary motor cortex, and (2) the presence of direct, monosynaptic cortico-motoneuronal connections (Xu, Haith, & Krakauer, 2015). Since both these principles are met in the UMN system for speech, as was mentioned earlier, lesions to this network will not only reduce muscle strength, but also interfere with the fine tuning of multi-articulator movements and lead to reduced dexterity of articulation. This deficit is probably often masked by the more deleterious effects of weakness and muscular overactivity in patients with severe spastic-paretic dysarthria. Yet, in the usually mild speech impairment of unilateral UMNS, "clumsy" articulation may emerge as a predominant symptom (Duffy, 2013).

Hemispheric Lateralization

There is a controversy about whether the corticobulbar system, with its bilateral organization, may exhibit a relative left lateralization for speech. In the motor cortex, hemodynamic activation lateralized to the left hemisphere has been demonstrated by functional neuroimaging during speech, but less so during non-speech tongue movements (Wildgruber, Ackermann, Klose, Kardatzki, & Grodd, 1996). Moreover, there is clinical evidence that left lateralization may also involve the descending corticobulbar fiber tracts. Urban et al. (2006) demonstrated that lesions within the face area of the primary motor cortex and along the course of the corticobulbar tract caused more severe dysarthria in patients with left as compared to right hemisphere infarctions. They concluded that there is at least a slight left dominance for articulation at the motor cortical level and the level of the descending white matter pathways. In a recent study based on magnetic resonance imaging (MRI) tractography of the corticobulbar tract in healthy adults, Liégeois, Butler, Morgan, Clayden, and Clark (2015) failed to find any evidence for *structural* or *functional* left asymmetry in their participants. However, this investigation was not based on brain activations for speech, but rather on a rapid syllable repetition paradigm that may involve speech-specific brain activity to a much lesser extent.

Another unresolved problem arising at this point is whether areas in the *left* primary motor cortex not only are specialized for more than simply the fine-tuning of articulatory agility (i.e., dexterity), but are also involved in higher-order speech planning mechanisms. In several case reports (e.g., Schiff, Alexander, Naeser, & Galaburda, 1983; Tanji et al., 2001), patients with lesions in the left ventral precentral region demonstrated a complex motor speech impairment that differed from dysarthria in two respects. First, the symptoms were not mild and transient, as one would expect in dysarthria resulting from circumscribed unilateral lesions, but were clinically remarkable and persisted over longer periods. Second, the described symptom patterns were more complex than one would expect from simply a weakness or clumsiness of the articulators—they rather resembled the pattern of apraxia of speech described in patients with more anterior left frontal lesions (see later discussion). This suggests that the prerolandic motor area representing the articulatory muscles has a more elaborate organization in the left than in the right hemisphere, and that left primary speech motor cortex (or a part of it) subserves similar motor planning functions as the areas immediately anterior to it, that is, ventro-lateral premotor cortex (BA 6), and adjacent posterior inferior frontal cortex (Broca's area, pars opercularis).

Emotional-Voluntary Dissociation

One of the most striking clinical observations related to paretic dysarthria resulting from lesions above the level of the cranial motor nuclei is that even severe bilateral damage to the corticobulbar system (e.g., in the so-called Foix-Chavany-Marie syndrome or in pseudobulbar palsy) may completely spare the motor functions of the speech musculature during emotional-expressive movements (i.e., in laughing or crying), while it destroys all volitional functions of the same muscles, including speech (e.g., Nowak, Griebl, Dabitz, & Ochs, 2010). A similar observation of an "automatic-voluntary" (better: "emotional-voluntary") dissociation may occur in individuals with unilateral UMN lesions. In these patients, voluntary lip functions (e.g., in cranial nerve examinations or in speech) are impaired by one-sided weakness of the lower facial muscles, although their spontaneous smiles are often perfectly symmetric (*volitional facial paresis*; e.g., Hopf, Müller-Forell, & Hopf, 1992). Together, these clinical dissociations are considered to evidence the existence of two independent pathways to the brain stem motor nuclei: a voluntary pathway originating in primary motor cortex, and a "limbic" pathway originating in the anterior cingulate cortex of the medial wall of the frontal lobe and mediating intrinsic or emotional-expressive movements of the speech muscles (see Figure 18.1). This latter system will be revisited later in this chapter (for a more comprehensive discussion, see Ackermann et al., 2014).

The Cerebellar Loop and Ataxic Dysarthria

Functional Topography

The cerebellum, situated in the posterior cranial fossa and connected with the brain stem via three pairs of cerebellar peduncles, is part of several loop systems interconnecting it with diverse cerebral cortical regions (Middleton & Strick, 2000). The most exhaustively studied cerebellar circuit is the motor loop, which interlinks, in a somatotopically organized manner, motor areas of the cerebral cortex with cerebellar motor regions in mostly the anterior, but also the posterior lobe of the contralateral cerebellar cortex. The motor loop comprises (1) a feedforward limb involving projections from primary motor cortex, ventral premotor cortex, and the SMA, traveling through pontine nuclei to the contralateral cerebellar hemispheres, and (2) a feedback limb via the deep cerebellar nuclei to the motor nuclei of the contralateral thalamus and further on to the motor areas of the cerebral cortex. Moreover, the cerebellum receives somatosensory information from oral and facial muscles via the trigeminal nuclei. By this afferent pathway, sensory information is channeled into cerebellar cortex, thus providing the cerebellar motor loop with information about the sensory state of the speech apparatus (for reviews of the pertinent literature, see Manto et al., 2012).

Through its topographic organization, the cerebellar motor loop is generally considered to implement an *inverse dynamics model* ("forward model"), which computes the motor commands needed to achieve a desired movement goal (Wolpert, Miall, & Kawato, 1998). As for speech motor control, more specifically, the cerebellum is known to be implicated in the evaluation of auditory and somatosensory error signals required in adaptation and compensation mechanisms (Golfinopoulos et al., 2011), as well as in the learning of novel articulations (Segawa, Tourville, Beal, & Guenther, 2014). These functions are essential for the acquisition, maintenance, and constant updating of a forward model of motor speech (e.g., Hickok, 2012; see Hickok, Chapter 20 in this volume). However, there is still no detailed account of the sensorimotor computations that the cerebellum performs during unperturbed speaking (see Tourville, Peeva, & Guenther, 2014, for a recent review).

Clinical Aspects

As originally described by Holmes (1917), lesions to the cerebellum may cause a movement disorder termed *motor ataxia*, that is, movement incoordination resulting in, among other things, overshooting or undershooting movements (*dysmetria*) and a decomposition of complex synergistic movements, as well as *dysdiadochokinesia* (i.e., slowing and irregular timing of repetitive movements). Ataxia is generally considered to reflect difficulties regulating the force, range, direction, velocity, and timing of muscle contractions, due to a dysfunction of the sensorimotor interactions mediating the feedforward and feedback control mechanisms involved in movement control.

Affliction of speech movements, resulting in *ataxic dysarthria*, may occur after lesions to predominantly the paravermal parts of the anterior cerebellum (Schoch, Dimitrova, Gizewski, & Timmann, 2006), for example, after infarctions of the superior cerebellar artery or in the course of degenerative disorders of the cerebellum (Brendel et al., 2013; Brendel et al., 2015). Regarding the lateralization of cerebellar ataxic dysarthria, a similar (though mirroring) situation subsists, as in the descending corticobulbar tract: lesions of both cerebellar hemispheres can cause dysarthria, but there seems to be a statistical preponderance of right cerebellar hemispheric involvement (Urban et al., 2003).

Ataxic dysarthria is characterized by respiratory, phonatory, and articulatory symptoms that appear much less predictable than those resulting from paresis: dyscoordination of respiratory muscles may lead to a "paradoxical" breathing pattern with unforeseen involuntary inspirations, voice quality and vocal pitch may undergo sudden changes, there may be voice tremor, and the precision of vowel and consonant articulations may vary between over- and undershooting realizations. Speaking is usually slow. Patients often compensate for dysmetria or cerebellar tremor by increased muscular tension (e.g., in the larynx) (for a comprehensive description of ataxic dysarthria, see Duffy, 2013).

Is There Cerebellar Speech Impairment beyond Dysarthria?

In the tradition of Holmes (1917), the consequences of cerebellar pathology have long been understood as exclusively motor or perceptuo-motor, which is compatible with the notion of ataxic dysarthria as a sensorimotor speech disorder. During the last few decades, however, the cerebellum has been discovered as an organ that is also implicated in cognition and emotion (Koziol et al., 2014), as well as in linguistic functions like syntactic processing, reading and writing, or verbal working memory (Mariën et al., 2014). This raises the question of whether cerebellar lesions may interfere not only with the motor execution aspects of speaking, but also with higher-order processes of speech sound production, such as phonetic or phonological planning, as discussed later in this chapter. As regards *phonological planning* impairment (i.e., phonemic paraphasia or phonemic jargon), there is not the slightest evidence from published case reports that problems of this kind may occur after cerebellar lesions (see Ziegler, 2015). However, a small number of studies have described symptoms resembling *phonetic planning* impairment (apraxia of speech) in patients with right cerebellar hypoperfusion (Mariën, Pickut, Engelborghs, Martin, & De Deyn, 2001; Mariën et al., 2006). As a primordial condition, however, these patients had focal lesions in the left cerebral hemisphere, which caused hypoperfusion in the contralateral cerebellum only secondarily (*crossed cerebellar diaschisis*). Hence, the left cerebral lesions found in these individuals may explain their speech impairments without any additional assumptions regarding a potential cerebellar contribution. As a conclusion, the implication of the cerebellum in sound production impairment seems indeed to be confined to the motor execution aspects of speech production (ataxic dysarthria) and does not encroach upon "higher" phonetic or phonological processes. This result constrains the *linguistic cerebellum hypothesis* and substantiates assumptions about the hierarchical organization of speech motor control in the brain (see Ziegler, 2015).

The Striatal Motor Loop and the Hypokinetic and Dyskinetic Dysarthrias

Functional Topography

As outlined in Figure 18.1, the descending speech motor pathway is also supported by a second, striatal (or basal ganglia) loop system. The basal ganglia are an assemblage of subcortical nuclei, consisting of the neostriatum (caudate nucleus and putamen), the globus pallidus, sub-thalamic nucleus, substantia nigra, and the nucleus accumbens. The basal ganglia are part of several parallel recurrent cortico-subcortical circuits subserving motor, cognitive, and motivational functions. They receive input from different neocortical areas and project back, via thalamic nuclei, to their respective cortical origins (Middleton & Strick, 2000). The basal ganglia loop implicated in sensorimotor control involves projections from multiple motor cortical areas—primary motor cortex, lateral premotor cortex, and the SMA—to the dorsal putamen, and back from the internal segment of the globus pallidus and the substantia nigra, via thalamic motor nuclei, to their motor cortical origins. At least two separate motor pathways can be distinguished within the internal connectivity of the basal ganglia: a direct, excitatory, and an indirect, inhibitory loop (Graybiel, 2000).

One other cortico-striato-thalamo-cortical circuit is important here, the so-called limbic pathway, connecting the basal ganglia with mesiofrontal cortical areas, especially anterior cingulate cortex and the SMA. Though the limbic and motor striatal loops are parallel circuits, they are also interconnected within the basal ganglia, thereby allowing motivational and affective input to influence the voluntary motor system (Ackermann et al., 2014; Turner & Desmurget, 2010).

According to widely accepted theories, the motor functions of the basal ganglia include primarily the scaling of movement speed and magnitude ("control of movement gain"; Turner & Desmurget, 2010), and the procedural learning of motor skills, especially motor sequence learning (Doyon & Benali, 2005). Both these functions are considered to be modulated, via the limbic striatal loop, by motivation- and emotion-related input (Turner & Desmurget, 2010).

Clinical Aspects

The two most representative clinical models of basal ganglia dysfunction are Parkinson's disease (PD) and Huntington's disease (HD) (see Copland & Angwin, Chapter 33 in this volume). In a simplified view, underactivity of the excitatory direct basal ganglia pathway leads to hypokinesia and bradykinesia in Parkinson's disease, resulting in poverty and slowing of movement, whereas underactivity of the inhibitory, indirect loop causes excess motor activity in Huntington's disease (hyperkinesia). These two pathomechanisms are also considered to be effective in the dysarthrias accompanying these disorders: Parkinson's dysarthria is mainly characterized by hypophonia (i.e., a soft, breathy, monotonous voice caused by hypokinesia of the respiratory-laryngeal system) and by imprecise or unintelligible articulation as a result of hypokinetic articulator movements. Huntington's dysarthria, on the contrary, presents with uncontrolled respiratory, laryngeal, and articulatory activity, resulting in highly dysfluent speech with sudden inspirations, irregular alterations of loudness and pitch, unwanted articulatory noises, and irregular over- or undershooting of articulations (for a more comprehensive description of the two syndromes, see Duffy, 2013).

Other speech syndromes have also been associated with basal ganglia pathology, for example, the dystonias (e.g., spasmodic dysphonia; Simonyan, Berman, Herscovitch, & Hallett, 2013) or vocal tics (McCairn et al., 2016).

Movement Gain Hypothesis of Parkinson's Dysarthria

In light of the gain control hypothesis of basal ganglia functions mentioned earlier, the paucity of respiratory, laryngeal, and vocal tract movements in Parkinson's dysarthria would be explainable as a problem of scaling the speed and size of these movements according to intrinsic motivation or external task requirements, that is, as a deficit in applying the appropriate "movement vigor" (Turner & Desmurget, 2010). Recall that the basal ganglia motor loop is strongly modulated by limbic cortical input via the ventral striatum, hence hypokinetic dysarthria in PD may accrue from a weakening of the link between motivation and movement gain (Ackermann et al., 2014). This model can explain several characteristics of Parkinson's dysarthria, for instance its strong dependence on situational parameters and its malleability through explicit instructions (Ho, Iansek, & Bradshaw, 1999), through motivational reinforcement (Ramig et al., 2001), or through strong external cues such as regularly structured rhythmical input (Späth et al., 2016).

Apart from Parkinsonism, the movement gain hypothesis of basal ganglia dysfunction and the interactions between the motor and the limbic striatal loops may also yield an explanation of inappropriate vocal behaviors and vocal tics, as they may occur, for instance, in Tourette syndrome. McCairn et al. (2016) ascribed these symptoms to a dysfunction of the parallel motor and limbic circuits of the basal ganglia, leading to a release of overshooting motor activity. This is consistent with observations of abnormal activation of paralimbic areas (e.g., anterior cingulate cortex) immediately preceding the onset of vocal tics (Bohlhalter et al., 2006). Hence, these data corroborate the view of the basal ganglia as an interface mediating human speech motor functions with the limbic vocalization system, as proposed by Ackermann et al. (2014).

Basal Ganglia Dysfunction and the Learning and Retention of Speech Motor Skills

According to available evidence, the basal ganglia are implicated in the procedural learning of motor skills, especially in motor sequence learning, but not in the long-term retention and recall of the acquired skills (Doyon & Benali, 2005; Turner & Desmurget, 2010). Considering speech as a sequential motor activity that is acquired throughout the first decade of life, the cortico-striatal-thalamic motor loop must play a major role in speech motor acquisition during childhood. Indirect evidence for this role was recently obtained in a morphometric study of bilinguals who acquired their second language either from birth or later during infancy (>5 years). The data pointed at significant gray matter changes in the left putamen as a function of the time of inception of learning and of articulatory proficiency in adulthood (Berken, Gracco, Chen, & Klein, 2015). This model is compatible with clinical findings that early basal ganglia pathology interferes massively with speech motor acquisition. As a matter of fact, early striatal lesions or genetic conditions interfering with the development of striatal nuclei have a devastating impact on speech acquisition in infants, as is known from case studies of patients with developmental apraxia of speech subsequent to *FOXP2* mutations (Vargha-Khadem, Gadian, Copp, & Mishkin, 2005). This syndrome does not occur after basal ganglia lesions affecting the adult brain, suggesting that the speech motor functions acquired during childhood are not permanently stored in the deep nuclei (see the following section). Hence, in adult speech, the striatal motor circuit is not involved in the planning or programming of articulations. As mentioned earlier, the basal ganglia circuit of the adult brain is rather implicated in the allocation of the amount of "movement vigor" corresponding with the speaker's emotional and motivational state and her or his perception of the environment. As elucidated in Ackermann et al. (2014) and in Ziegler & Ackermann (2017), the contribution of the basal ganglia obviously undergoes substantial changes during the maturation of speech motor skills.

Left Posterior Inferior Frontal Cortex and Apraxia of Speech

Functional Topography

According to a long tradition, the posterior part of the inferior frontal gyrus in the left hemisphere is viewed as a site where higher-order speech motor information is stored. However, there is a lasting controversy about exactly which regions of left frontal cortex are implied: Broca's area (pars opercularis), caudally neighboring premotor cortex, primary (rolandic) motor cortex, or anterior insular cortex (Graff-Radford et al., 2014; Richardson, Fillmore, Rorden, Lapointe, & Fridriksson, 2012). A contribution of one or more of these regions to motor speech has primarily been inferred from lesion studies of patients with articulation disorders, but there is an increasing number of functional imaging studies pointing at the left anterior perisylvian cortex as a core region of speech motor planning (e.g., Bohland, Bullock, & Guenther, 2010; Riecker, Brendel, Ziegler, Erb, & Ackermann, 2008). Although it is usually the entire speech motor network in the brain that is activated in these studies, the posterior inferior frontal region of the left hemisphere is deemed to dominate the motor output system via efferent connections with, inter alia, the neighboring ventral premotor region, the cerebellum, and the striatum (Eickhoff, Heim, Zilles, & Amunts, 2009).

The motor information traded in left inferior frontal cortex and/or ventral premotor cortex is often termed *speech motor plans* or *programs*, or *phonetic plans*. In the light of what was said earlier about striatal motor learning capacities, one may hypothesize that the speech-specific motor information acquired during childhood through striatal functions is ultimately retained in these cortical areas (Ackermann et al., 2014; Ziegler & Ackermann, 2017), either in the form of holistic motor plans for syllables or other speech units, or as acquired implicit knowledge about how articulatory gestures are typically combined in a speaker's native language (Ziegler, Aichert, & Staiger, 2012).

Of note, the anterior speech motor region in the left brain is at the front end of a recurrent network connecting, via subcortical fiber tracts, the auditory association areas in superior temporal cortex with the frontal speech motor areas, with a relay area at the parieto-temporal junction. This connectivity has been termed the *auditory dorsal pathway* (e.g., Hickok & Poeppel, 2004; Rauschecker, 2011; see Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume). Without going into the details of this rapidly expanding theory, a subsegment of the dorsal pathway, connecting the superior temporal gyrus to the premotor cortex via the arcuate fascicle and the superior longitudinal fascicle, is supposed to map auditory onto motor representations and thereby contribute to phonological processing in the production and perception of speech (Amunts & Zilles, 2012; Murakami, Kell, Restle, Ugawa, & Ziemann, 2015). On this account, the auditory dorsal pathway can be considered as the anatomical substrate of an internal model subserving motor speech through forward and inverse mappings of sensory and motor representations (e.g., Hickok, 2014; see Hickok, Chapter 20 in this volume). Within this structure, the left parieto-temporal zone is viewed as a region where sensorimotor speech information can be buffered through internal rehearsal (Buchsbaum & D'Esposito, 2008).

Clinical Aspects

Patients suffering from lesions to the left anterior peri- and sub-sylvian regions mentioned in the preceding may suffer from a speech motor impairment termed *apraxia of speech* (AOS). This syndrome is predominantly characterized by articulation problems, with no or only minor phonatory and respiratory involvement. The patients produce mispronounced ("phonetically distorted") consonants and vowels, but also phoneme errors sounding well articulated (e.g., *shrosh* for *frosch*, German "frog"). Their speech is effortful and dysfluent due to frequent occurrences of articulatory groping, false starts, and re-starts. The occurrence of speech errors and dysfluencies is influenced by a number of factors, such as syllable complexity, syllabic length, syllable frequency, or metrical structure (Aichert, Späth, & Ziegler, 2016; Staiger & Ziegler, 2008) (for detailed descriptions of the clinical pattern of AOS, see Ziegler, 2008).

AOS is distinguished from the dysarthrias on several grounds. One specific property of AOS is that it is a motor speech impairment that is strongly lateralized to the dominant hemisphere. As mentioned earlier, this is not the case in the dysarthrias, which may result from lesions to either hemisphere and are mostly mild and transient after one-sided lesions. Another point is that the speech pattern of apraxic speakers cannot be explained by any of the pathomechanisms underlying known neurologic movement disorders (i.e., paresis, ataxia, hypokinesia, tremor, or the like). A sign that is particularly incompatible with these "elementary" motor dysfunctions is the high variability of apraxic errors and the occurrence of error-free productions, even in patients who are moderately impaired (Staiger, Finger-Berg, Aichert, & Ziegler, 2012).

The term *apraxia* dates back originally to Liepmann, who termed the speech impairment of a patient suffering from limb apraxia as an "apraxia of the language muscles" (Liepmann, 1900, p. 129) because the patient's speaking behavior and error pattern reminded him of limb apraxia. Since Broca's first description of a case of "speechlessness" (*aphémie*), the presumed nature of the motor impairment underlying AOS has been characterized variably as a "loss of movement memories," a "motor programming disorder," "phonetic disintegration," a dissolution of "coordinative structures," or a destruction of "phonetic/motor plans"—depending on the actual psycholinguistic and motor theories of each time (Ziegler et al., 2012). Yet, there has always been a broad consent about the superordinate, higher-order character of the speech impairment resulting from corruption of left inferior-frontal motor mechanisms.

Apraxia of Speech versus Phonological Impairment

From a clinical viewpoint, there is often a problem of discriminating AOS from a speech sound disorder termed *phonological impairment*, which occurs in patients with various types of aphasia (Butterworth, 1992; Schwartz, 2014). The main symptom of this impairment is phonemic paraphasia, that is, the occurrence of phoneme substitutions, deletions, additions, or metatheses (e.g., *film* → *flim*). Unlike in AOS, where such errors can also be observed, the phonemic paraphasias of aphasic patients are typically well articulated, and the afflicted patients usually speak more fluently, with no articulatory groping, and with less effort. Problems of differentiating between the two syndromes arise from the fact that their symptoms overlap; that is, AOS patients, like patients with phonological impairment, produce errors that are perceived as well articulated, and patients with phonological impairment may at times be considerably dysfluent, similar to AOS patients, due to their "conduite d'approche" attempts and self-corrections. Moreover, the occurrence of errors is modulated by similar factors in both syndromes (i.e., word length, syllable complexity, and syllable frequency) (Galluzzi, Bureca, Guariglia, & Romani, 2015).

The two types of sound production impairment have in common that they result from lesions along the left auditory dorsal pathway: While AOS is caused by lesions to the frontal target areas and the anterior segment of the arcuate and superior longitudinal fascicles (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013), phonological impairment is associated with damage to the more posterior parts (i.e., the posterior superior temporal and inferior parietal lobes, the parieto-temporal region, or their connecting fiber bundles) (Schwartz, Faseyitan, Kim, & Coslett, 2012). In the cognitive neurolinguistic tradition, phonological impairment is subdivided into a lexical and a post-lexical subtype and is ascribed to a processing level where phonological form information is retrieved, traditionally with the assumption that the underlying representations and mechanisms are abstract and symbolic (Goldrick & Rapp, 2007; see Rapp & Purcell, Chapter 17 in this volume). Considering the functional topography of the auditory dorsal pathway, however, one would speculate that the mechanisms implied in phonological impairment deal with auditory-motor integration processes rather than with amodal symbols—a view supporting substance-based rather than abstractionist approaches to phonology (Buchsbaum et al., 2011; Hickok, 2012). From this perspective, the syndromes of the left auditory dorsal stream can be considered as a clinical model of the phonetics-phonology interface (for references and a discussion, see Ziegler, 2016).

SPEAKING—A TASK-SPECIFIC MOTOR ACTION?

A controversial theoretical issue is about where the motor speech disorders find their place between movement and language. This question hooks up with discussions regarding the specific tuning of the vocal tract and respiratory-laryngeal motor systems for the production of spoken language. Broadly speaking, two opposing views are discussed:

1. Speaking is grounded in a universal, domain-general motor proficiency of the movement organs implied in speaking. It engages the same neural mechanisms as any other "non-speech" or "speech-like" vocal tract motor task, such as isolated tongue protrusion, visuomotor tracking by the jaw or tongue, sustained vowel production, maximally rapid syllable repetitions, and so forth. All these tasks involve individual combinations of *universal* motor skills based, for instance, on timing, coordination, force generation, and so forth. Damage to the neural network subserving these properties will therefore compromise all motor activities of the vocal organs. As a corollary, clinical assessment and treatment of motor speech disorders need not necessarily be based on speaking, but can principally also employ non-speech tasks (Ballard, Granier, & Robin, 2000; Ballard, Robin, & Folkins, 2003).
2. Motor speech relies on a highly specialized neural organization of the movements implied in speaking. The domain-specific organization of the motor act of speaking results from extensive motor exercise during the long period of speech acquisition, which—like all other types of motor learning—has an impact on the structural and functional organization of the underlying neural network. Motor skill learning is known to go hand in hand with organization processes at all levels of the brain's motor network: cortical and subcortical, gray and white matter, structural, topographic, as well as synaptic (Adkins, Boychuk, Remple, & Kleim, 2006; Doyon & Benali, 2005), suggesting that after more than a decade of infant speech motor learning (Kent & Vorperian, 1995), the neural network engaged in speech motor control must be highly specialized. Another unique aspect of speaking is that its motor organization is inseparably entrenched with auditory perception, both in acquisition and in the mature system (Hickok, 2014), which is not the case for chewing, isolated lip pursing, visuomotor tracking, and so forth. As a consequence, brain lesions may impair speech and leave other motor functions largely intact, or vice versa. Therefore, clinical assessment and treatment approaches based on non-speech oral motor tasks are inappropriate (Ziegler & Ackermann, 2013).

In the following sections, we will revisit the pathomechanisms of motor speech disorders from the perspective of whether and how they interfere with speech-specific aspects of oral motor control and will provide explanations for the clinical findings of dissociated speech and non-speech oral motor impairments (Staiger, Schölderle, Brendel & Ziegler, 2017).

Upper Motor Neuron Dysfunction

Primary motor cortex is among the most extensively examined sites of practice-related neural plasticity (e.g., Doyon & Benali, 2005; Monfils, Plautz, & Kleim, 2005).

According to Adkins et al. (2006), plasticity mechanisms also include the descending fiber tracts projecting onto the motor nuclei. Of particular concern with regard to speaking are investigations of plasticity mechanisms associated with motor learning initiated early in childhood and extending over long periods, as in some professional musicians and athletes. These studies have consistently revealed substantial practice-related modifications of cortical motor maps (Gaser & Schlaug, 2003) and descending fiber tracts (Imfeld, Oechslin, Meyer, Loenneker, & Jancke, 2009). Though the neural plasticity mechanisms associated particularly with speech motor learning during infancy are not accessible to direct investigations, electrocortigraphic (ECoG) recordings of neuronal activity during speaking reported by Bouchard et al. (2013) revealed syllable-specific patterns that can only be explained as a result of learning-induced cortical plasticity. On the basis of this evidence, one would conjecture that especially the fine motor skill aspects of speaking, relying on the integrity of such motor maps and of the monosynaptic corticobulbar pathway, are particularly vulnerable to speech-specific motor impairment (see earlier discussion in this chapter). Symptoms related especially to these properties may therefore be inaccessible to non-speech assessment and treatment approaches. On the contrary, lesions to the indirect, polysynaptic corticobulbar fiber tracts, with their concomitant alterations of muscle tone and posture in spastic-paretic dysarthria, may lead to less specific symptoms because this phylogenetically older system is probably less malleable through motor plasticity mechanisms. Since brain lesions most often involve both the direct and the indirect corticobulbar pathways, speech–non-speech dissociations are often masked.

Cerebellar Dysfunction

Like the primary motor cortex, the cerebellum is also subject to practice-induced plasticity (Doyon, Penhune, & Ungerleider, 2003); hence its structure and function must also be considered to be shaped in specific ways during speech motor acquisition. The contribution of the cerebellum to motor learning is known to be particularly distinct during the fast, early learning phase. During the further course of learning and consolidation, its major activation shifts from the cerebellar cortex to the deep cerebellar nuclei and further on to other motor centres of the brain (Doyon et al., 2003). This entails that cerebellar dysfunction will have a differential impact on novel motor tasks, such as the tracking of a moving cursor through tongue or jaw movements, as opposed to overlearned motor skills, such as speaking.

Regarding the ataxic pathomechanism resulting from cerebellar lesions, some movement types are, in addition to being unlearned, also known to be particularly vulnerable to motor dysfunctions. Among these are motor tasks requiring rapid sequential inversions of agonist and antagonist movements (*diadochokinesis*), maintenance of a fixed posture over longer periods, or minute online adaptations of motor output to a slowly moving target (*visuomotor tracking*). These tasks call for highly adaptive sensorimotor mechanisms to maintain a static target position, track a moving target, or optimize strategies for fast repetition, and are therefore particularly prone to cerebellar pathology (e.g., Miall & Reckess, 2002).

Tasks of these types also play a prominent role in experimental and clinical assessments of neurological speech disorders: rapid repetitions of sequential or alternating syllables (e.g., "puh-puh-puh," "puh-tuh-kuh") constitute a vocal tract variant of diadochokinesis; sustaining a vowel or fricative for several seconds represents phonatory or articulatory variants of motor persistence tasks; and tracking a moving target on a computer screen by appropriate adaptations of jaw or tongue forces is a variant of visuomotor tracking. Like in the limbs, these tasks are particularly sensitive to cerebellar involvement: for instance, patients with cerebellar pathology were found to be disproportionately slow in oral diadochokinesis relative to speaking (Brendel et al., 2015; Ziegler & Wessel, 1996). Furthermore, cerebellar patients are often highly conspicuous for irregular pitch and loudness or voice tremor in sustained vowel production, although these symptoms are much less remarkable or even absent during speech, where maintenance of stable postures is not a critical requirement (Ackermann & Ziegler, 1994). Finally, patients with cerebellar ataxia were found to demonstrate severe impairment of visuomotor airflow tracking that was, however, uncorrelated with their dysarthric impairment (Deger, Ziegler, & Wessel, 1999). Obviously, clinical examinations based on such tasks are not particularly predictive of the severity of cerebellar dysarthria, first because they are unlearned, and second because the motor organization of speaking does not rely on the specific requirements of these oral/vocal motor tasks.

Striatal Dysfunction

As mentioned earlier, there is a shift in striatal motor functions from the acquisition to the mature stage of speech motor control, with a major role in the learning of the sequential and coordinative aspects of speaking during infancy, and predominantly a gain-control function in adulthood (Ziegler & Ackermann, 2017). This entails—like in the cerebellar system—a fundamental difference of striatal motor functions between tasks with a high proficiency level, such as adult speech, and others that are new and subject to immediate motor learning mechanisms, such as maximum performance or visuomotor tracking tasks. There is even evidence that motor tasks relying on habituated or automated skills, like speaking, and others relying on attentive, goal-directed control, like visuomotor tracking, are differentially organized within the basal ganglia and may therefore dissociate in striatal dysfunction (Redgrave et al., 2010). In an experimental investigation of Parkinson's patients, Connor and Abbs (1991), for instance, found marked differences in jaw movement performance for patients with Parkinson's disease between a visually guided tracking task, a rapid syllable repetition task, and speaking. The smallest deviations from normal, in terms of movement cycle durations, occurred in the speech task, and the largest deviations in the tracking task, which is consistent with differences in novelty/unfamiliarity between the three experimental settings and demonstrates that striatal dysfunction has a differential effect on learned versus novel oral motor tasks.

However, there may also be a more universal aspect of striatal dysfunction in vocal/oral motor control and speech. As regards the gain control hypothesis of striatal motor regulation and the influence of the limbic striatal loop, a plausible assumption is that impairment of this mechanism may indeed have a more universal effect across different motor activities. More specifically, such a dysfunction probably involves nonverbal emotional facial and vocal expression in the first place (e.g., Parkinsonian "hypomimia"), and rubs off on speech or other voluntary oral movements only in the second place. Likewise, motor disinhibition phenomena resulting from excess limbic discharge across the ventral striatum (vocal and facial tics; cf. McCairn et al., 2016), or from overactivity of the direct striatal pathway, may also exert unspecific influences on speech and other vocal and oral motor activities, through a generalized excitation of motor output channels.

Apraxia of Speech

Assuming, as suggested earlier, that the left ventral premotor and anterior opercular region is a site where learned motor routines for speaking are stored, one would expect that lesions to this area result in speech impairment that is deeply moulded by the linguistic (i.e., phonological) patterning of words and phrases. This is indeed the case: Numerous factors are known to influence the occurrence of speech errors in apraxia of speech that are related to phonological and statistical aspects of speech, for instance syllable frequency and syllable structure (Aichert & Ziegler, 2004; Staiger & Ziegler, 2008), or metrical rhythm (Aichert et al., 2016). Studies investigating the relearning of syllables and words in apraxic speakers have revealed that learning and transfer in these patients is strongly constrained by phonological structure (e.g., syllable constituency) (Schoor, Aichert, & Ziegler, 2012), which is compatible with findings that speech motor learning in healthy populations is extremely local and sensitive to phonological context (Tremblay, Houle, & Ostry, 2008). We have recently proposed a model of speech motor planning based on data from apraxic speakers that explains the phonetic planning demands for spoken words by a hierarchical architecture, expanding from articulatory gestures over syllable constituents to metrical structures (Ziegler & Aichert, 2015). Such a design cannot plausibly be based on domain-general motor mechanisms, but must necessarily result from an implicit, statistical learning of the motor routines associated with the phonological forms that are pervasive in a speaker's language. The view of apraxia of speech as an impairment of the acquired motor capacities involved in speaking is compatible with clinical findings pointing at double dissociations between apraxia of speech, on the one hand, and apraxia of non-speech movements ("oral-facial apraxia"), on the other (cf. Bonilha, Moser, Rorden, Baylis, & Fridriksson, 2006; for references see Ziegler, 2003).

CONCLUSIONS

Motor speech disorders result from dysfunctions of the neural network engaged in the control of speech movements, that is, a descending corticobulbar pathway supplemented by a cerebellar and a striatal motor loop and dominated by a left-lateralized inferior-frontal and ventral premotor planning center connected with auditory speech areas in the left temporal lobe. The voluntary motor system engaged in speaking is modulated by motivational and affective input from mesiofrontal cortex and limbic brain regions. The symptoms observed in the different motor speech disorders reflect the motor control mechanisms of the particular brain sites involved in different neurologic conditions, but they also express compensatory mechanisms evolving in reaction to the respective impairments.

Speech impairment caused by neurologic dysfunction should be understood as a condition affecting motor functions that are specifically dedicated to verbal communication. This view is substantiated predominantly by evidence from studies of learning-related neural plasticity. Yet, there may also be domain-general pathomechanisms affecting speech motor control in dysarthria, such as generalized alterations of tone and posture in spasticity or dysregulation of limbic activation in basal ganglia disorders. Many of these points have not yet been substantiated by empirical evidence and still wait for clinical approval.

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CHAPTER 19

INVESTIGATING THE SPATIAL AND TEMPORAL COMPONENTS OF SPEECH PRODUCTION

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INTRODUCTION

To date, two major behavioral approaches have been utilized in speech-production research. The first involves characterizing speech errors or dysfluencies produced either spontaneously, experimentally, and/or as a consequence of brain injury (i.e., aphasia). The second entails experimental investigations of the time course of speech production in different contexts by means of response-time analyses. These psycholinguistic approaches have been complemented recently by a third, involving the application of electrophysiological, neuroimaging, and brain stimulation technologies, following from the realization that we require a better understanding of the neural mechanisms underlying the behavioral data. Theoretical accounts of speech production have also begun to incorporate neural mechanisms in their feature set, although most remain limited to explaining specific effects observed during performance of particular paradigms. However, application of these technologies involves surmounting methodological challenges not typically encountered in studies of language comprehension, largely due to speech-related artifacts introduced by articulation and breathing.

In this chapter, we provide an overview of relevant spatial and temporal components of language production. We then review findings from a range of studies investigating language production in brain-lesion patients and healthy participants, with an emphasis on evidence from context manipulations in picture-naming paradigms designed to identify and characterize core processes and components of the network involved in retrieving words from the mental lexicon. Boxes 19.1–19.4 address the methodological

Box 19.1 Methodological Challenges for Investigations of Speech Production

From a methodological perspective, neurolinguistic investigations of speech production are inherently more complicated to conduct than those targeting nonlanguage processes and/or comprehension. Two of the most widely employed technologies, functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume) and neurophysiological recordings via electroencephalography and magnetoencephalography (EEG and MEG, respectively; see, in this volume, Leckey & Federmeier, Chapter 3, and Salmelin, Kujala, & Liljeström, Chapter 6) are especially sensitive to speech-related signal artifacts that compromise data quality and confound interpretations. Consequently, the overwhelming majority of studies using these technologies have examined the production of single words or short phrases. The nature of these speech-related artifacts and the appropriate data acquisition and analysis techniques to ameliorate them are briefly described in Boxes 19.2 and 19.3.

The earliest, and perhaps most intuitive, approach to dealing with speech production artifacts in fMRI and electrophysiological studies was to avoid them entirely. In the first fMRI studies conducted in the 1990s, participants were typically instructed to respond *covertly* (i.e., use *inner* speech). Aside from the obvious problem of having no behavioral data to confirm the presence of a significant psycholinguistic effect, later studies comparing covert and overt speech within the same paradigm revealed engagement of different cerebral regions. However, the relative contributions of those areas are difficult to interpret (for example, greater engagement of regions during overt production might represent syllabification and articulatory-motor processes, while covert production might additionally engage domain general processes such as response inhibition and self-monitoring while reducing activity in production-related regions; see the review by Indefrey & Levelt, 2004). Thus, it became clear that avoiding speech-related artifacts by requesting covert responses from participants was not the optimal strategy.

challenges that need to be surmounted by speech-production researchers in order to provide valid and reliable data.

SPATIOTEMPORAL COMPONENTS RELATING TO PROCESSING STAGES IN SPEECH-PRODUCTION MODELS

Based upon speech error and response time data, models of spoken-word production have stipulated that the processing stages involved in producing words include *perceptual and conceptual preparation*, *lexical selection*, *word-form encoding*, and *articulation*. Indefrey and Levelt's (2000, 2004) influential review and meta-analysis represented the first serious attempt to relate neuroimaging and electrophysiological data to these processing stages. In 2004, the electronencephalography (EEG) and

Box 19.2 Methodological Challenges for Neuroimaging Investigations

In fMRI, the physical act of producing speech introduces blood oxygenation level dependent (BOLD) signal changes during continuous imaging, necessitating a different approach to data acquisition. These task-correlated, speech-induced signal changes are not a consequence of neural processes, although they tend to mimic or mask them as they occur over the perisylvian cortex, and are not limited to the speech act itself—they contaminate subsequent images acquired in a functional time series. They also do *not* merely reflect whole-head rigid body motion, and persist following the application of standard image-realignment algorithms. However, it is not uncommon to read papers in which authors claim to have inspected their realigned data and confirmed that it was free from speech related artifacts. Rather, signal changes from producing even a single word during continuous imaging reflect movement-by-magnetic-susceptibility *interactions*. Areas of magnetic-susceptibility-related signal variation are located in inferior temporal and frontal cortices, where air-bone-tissue interfaces exist, and are problematic for both structural and functional MRI. Producing speech worsens these susceptibility-related artifacts by increasing geometric distortions, losing *and* introducing signal—the latter from regions within and immediately outside the field of view linked to muscle movement. A relatively reliable finding is that articulatory muscle movement produces a rapid signal decrease in and around Broca's area and its right hemisphere homologue, compromising any task-related signal changes (see Mehta, Grabowski, Razavi, Eaton, & Bolinger, 2006). Consequently, the BOLD signal in continuous fMRI acquisitions is unavoidably compromised during speech production, and the simultaneous gradient noise often impedes recording and measuring of accuracy and speech-onset latencies. It is therefore essential to adopt well-validated, alternative approaches. As we will note later, some of the inconsistencies in reported fMRI findings for speech production paradigms can be directly attributed to inappropriate acquisition methods.

In the first decade of the 2000s, a concerted international research program demonstrated the utility of a different image-acquisition method for speech production fMRI studies, now broadly referred to as *sparse temporal sampling*. In brief, the technique involves acquiring only a single fMRI volume *after* each utterance, timed to capture the estimated peak BOLD signal response. As speech is produced during relative silence (i.e., without gradient noise associated with image acquisition), both accuracy and latency are able to be measured reliably (see de Zubicaray, Wilson, McMahon, & Muthiah, 2001). Independent validation studies subsequently confirmed that the technique is able to acquire artifact-free images during spoken-word production (Gracco, Tremblay, & Pike, 2005), and showed that neural activity patterns during non-speech paradigms are comparable for sparse and continuous imaging acquisitions (Nebel et al., 2005). Note that the technique requires relatively long inter-trial intervals, and BOLD signal time-course data are not available. However, hemodynamic time-course information is rarely analyzed, even in fMRI studies using continuous imaging whose primary purpose is to provide spatial information.

Another recently introduced fMRI acquisition method that shows promise for investigating speech production is arterial spin labeling (ASL), which detects increases in cerebral perfusion associated with task performance. Continuous perfusion imaging acquisitions are demonstrably less sensitive to speech-related susceptibility artifacts than BOLD fMRI (Kemeny, Ye, Birn, & Braun, 2005), and so may prove useful for sentence-production paradigms. Although the sensitivity and temporal resolution of ASL are typically lower than BOLD acquisitions, there is less inter-individual variability in perfusion signal changes compared to the BOLD signal, resulting in increased sensitivity to group-level effects (Detre, Rao, Wang, Chen, & Wang, 2012).

Box 19.3 Methodological Challenges for Electrophysiological Investigations

Until recently, the dominant approach in electrophysiological (here collectively defined as EEG and MEG; see, in this volume, Leckey & Federmeier, Chapter 3, and Salmelin, Kujala, & Liljeström, Chapter 6) studies of speech production has been to analyze data time-locked to stimulus onset (e.g., a picture to be named) up to an arbitrary point before articulation (e.g., 400 ms; see Ganushchak, Christoffels, & Schiller, 2011). Muscle activity associated with mouth, head, and eye movements are well-known sources of artifacts that confound EEG and MEG recordings. Yet, myogenic and speech-related breathing artifacts can in fact precede production by as much as 500–600 ms (e.g., Brooker & Donald, 1980; Galgano & Froud, 2008). Several approaches to measuring and correcting for speech-related artifacts have since been proposed and adopted, including using electromyogenic (EMG) recordings from the mouth/lip (e.g., Ouyang et al., 2016; Porcaro, Meaglia, & Krott, 2015; De Vos et al., 2010). In addition to stimulus-locked analyses, recent studies have also begun analyzing ERPs locked to articulation onset (e.g., Riès, Xie, Haaland, Dronkers, & Knight, 2013). However, it is important to note that response-locked ERPs are sensitive to onset differences due to phonetic features (e.g., /b/ and /p/ onset words vary by about 40 ms; Fargier, Bürki, Pinet, Alario, & Laganaro, 2017), so balanced designs are essential.

Additional sources of variability are encountered in intracranial EEG studies of speech production (for a review, see Llorens, Trébuchon, Liégeois-Chauvel, & Alario, 2011). These studies are typically conducted in candidates for epilepsy surgery who have intractable seizures. This necessitates comprehensive language assessments for each patient to characterize his or her cognitive function, and investigations to be performed in medication- and seizure-free periods. Due to clinical constraints, electrode placement is often inconsistent across patients within a study, a problem referred to as *sparse sampling* (not to be confused with the fMRI acquisition technique).

As Piai, Riès, and Knight (2015) noted in their commentary, a major issue in the electrophysiological literature on speech production has been variability in reporting analysis steps and suboptimal statistical testing. In particular, a number of studies appear to lack procedures for correcting speech-related artifacts. Moreover, electrophysiological data are multidimensional (i.e., many channels can be analyzed at multiple time points), which requires analysis strategies that take into account this multiple-comparison problem. However, a number of studies have adopted inappropriate statistical methods for dealing with this problem (see Piai, Dahlslätt, & Maris, 2015). These factors have likely contributed to the lack of consistency among some of the reported findings we discuss later.

magnetoencephalography (MEG) literature on picture naming and word production was scant compared to neuroimaging studies (functional magnetic resonance imagining [fMRI] and positron emission tomography [PET]), and the available data reflected a mix of covert and overt production. In 2011, Indefrey reviewed the literature for new studies and provided an updated version of the time course of these processing stages and the corresponding brain regions. According to this updated version, and assuming a response time of 600 milliseconds (ms), perceptual and conceptual preparation reliably involve the ventral surface of the temporal-occipital cortex. Perceptual preparation (given a visual or auditory stimulus) is completed around 100–150 ms after stimulus

Box 19.4 Methodological Challenges for Brain Stimulation Techniques

Brain stimulation methods have also seen increasing application to investigate speech production. Noninvasive techniques include transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume) and transcranial direct current stimulation (tDCS; for review, see Hartwigsen, 2014), while direct electrical stimulation (DES) is invasive and most frequently used intraoperatively for surgical planning (see Duffau, Chapter 8 in this volume). Brain stimulation methods are useful for studies of language production because researchers can modulate brain activity, and even temporarily disrupt the function of a targeted region (see Schuhmann, Chapter 5 in this volume), and examine what impact this has on task performance. Brain stimulation studies therefore provide an additional dimension of information regarding the necessity of a brain region for task performance. For both tDCS and TMS, effective sham approaches are able to blind participants to the stimulation conditions. Like TMS, online and offline stimulation protocols are possible with tDCS. However, it has been proposed that they differ in terms of their effects on neural activity: the former is thought to modulate a specific network involved in task performance, while the latter likely produces modifications to a broader network of neural activity that lasts beyond the period of stimulation (Miniussi, Harris, & Ruzzoli, 2013). The latter approach may therefore be less relevant to the study of psycholinguistic effects. The two modes of stimulation present a challenge in terms of reporting and interpreting effects in neurolinguistic studies. In particular, findings from offline and online studies should not be discussed synonymously in terms of replications. Ideally, a comparison of offline and online protocols in the one study would be most informative.

Of the three techniques, tDCS is less well established from a methodological perspective, and the validation of specific protocols in both healthy participants and aphasic patients requires further research attention. Inconsistencies in reported findings appear attributable to variability in protocols applied across studies, including departures from standard experimental paradigms (e.g., Westwood, Olson, Miall, Nappo, & Romani, 2017; see Gauvin, Meinzer, & de Zubicaray, 2017, for comment). The tDCS technique involves applying a weak electrical current between scalp-affixed electrode pads to modulate resting membrane potentials on the cortical surface. These pads are typically 5 x 7 cm, although high-density electrode sets are now being marketed by some manufacturers. Localization of effects in behavioral studies is therefore inexact, dependent on electrode placement. Combined tDCS-fMRI studies show promise in terms of localizing effects beneath electrodes (e.g., Meinzer, Yetim, McMahon, & de Zubicaray, 2012). Unlike TMS, tDCS is not able to provide information about the timing of functionally relevant brain regions. Likewise, in the case of DES, the clinical setting does not easily afford timing investigations given that the stimulation cannot be applied systematically at different time points during stimulus presentation.

onset, whereas conceptual preparation is completed around 200 ms. The mid-section of the lateral middle temporal cortex is reliably involved in lexical-semantic (*lemma*) processing, and the posterior superior and middle temporal cortex (Wernicke's area) in phonological word form (*lexeme*) retrieval. These processing stages span between 200–290 ms and 290–370 ms, respectively. Correlates of post-lexical stages of processing, including syllabification at 355–475 ms, phonetic encoding at 455–600 ms, followed by motor articulation, were found to encompass both left inferior frontal gyrus (IFG) and premotor cortices (for a review of these latter mechanisms, see Tremblay, Deschamps, & Dick, Chapter 15 in this volume). Finally, Indefrey and Levelt (2004) ascribed the monitoring of both internal and external speech to bilateral superior temporal gyrus (STG), noting the prolonged activation observed in these structures. However, Indefrey (2011) later acknowledged that self-monitoring processes likely engage a more comprehensive network involving the anterior cingulate cortex (ACC) and supplementary motor area (SMA), perhaps reflecting more domain-general mechanisms, an issue we will return to later.

This account of the relative timing of brain regions engaged during production has been challenged by recent reviews. For example, Llorens, Trébuchon, Liégeois-Chauvel, and Alario (2011) reviewed intracranial EEG studies, noting that the findings were not always consistent with the earlier scalp-recorded EEG and MEG findings. In particular, they did not find consistent evidence for the involvement of the mid-portion of the middle temporal gyrus (MTG) linked with the time window for lexical-semantic processing, and noted much earlier engagement of motor cortex and IFG (from 200 ms), challenging an interpretation of the latter regions' roles in terms of only post-lexical processes. Recently, Munding, Dubarry, and Alario (2016) reviewed 20 years of MEG research on speech production, and concluded that while the data broadly supported the conclusions of Indefrey and Levelt's meta-analyses, the evidence was not consistent with a serial processing architecture, but rather suggested parallel activation. In addition, they presented evidence of very early activation of IFG and motor cortex in some studies, which they attributed to top-down control and selection processes. This review provoked considerable debate (see responses by Piai, 2016; Riès, 2016; Strijkers, 2016). A relatively consistent criticism was that Munding and colleagues reviewed studies with different experimental manipulations that elicited much longer production latencies than the 600 ms assumed by Indefrey and Levelt, blurring the temporal estimates for the processes in question. Therefore, the study by Munding et al. (2016) is inconclusive with respect to the question of serial versus parallel processing in spoken-word production. Another recent critique by Strijkers and Costa (2016) likewise advocated parallel over serial processing, and invoked top-down selection and control processes within the framework of a neural assembly rather than a chronometric model (but see the response by Indefrey, 2016).

Despite the emphasis on electrophysiological recordings to inform the temporal components of speech production, research with single- and multiple-pulse transcranial magnetic stimulation (TMS) has afforded additional information about the *critical* or *necessary* timing of the brain regions in the production network. A number of studies have consistently targeted left IFG/Broca's area and have employed picture naming (e.g., Chouinard, Whitwell, & Goodale, 2009; Schuhmann, Schiller, Goebel, & Sack, 2009, 2012; Wheat et al., 2013). Across these studies, TMS reliably slowed naming latencies when applied to the left IFG 300–400 ms following picture presentation, consistent with Indefrey's (2011) updated account. Critically, when TMS was applied to left IFG at 100–200 ms following picture onset (i.e., the time window of early activation reported in some MEG studies; see Munding et al., 2016; Strijkers & Costa, 2016), naming latencies were *not* significantly affected (Schuhmann et al., 2009, 2012; Wheat et al., 2013). Therefore, if early activation of IFG is attributable to top-down selection and control mechanisms, as some authors propose, then the consistent finding from TMS studies does not support the necessary early involvement of these processes in simple picture naming. The same can be said for the early involvement of motor cortex based upon some MEG results (e.g., Munding et al., 2016; Strijkers & Costa, 2016), with two TMS studies consistently failing to observe effects of stimulation of the motor cortex on naming latencies at 0, 100, or 300 ms after picture onset (Mottaghy, Sparing, & Töpper, 2006; Töpper, Mottaghy, Brugmann, Noth, & Huber, 1998).

To our knowledge, three TMS studies of picture naming have targeted Wernicke's area at the 200–300 ms time period identified by Indefrey (2011) as corresponding to phonological word form retrieval (Mottaghy et al., 2006; Schuhmann et al., 2012; Töpper et al., 1998). Surprisingly, *none* reported a significant effect on naming latencies, although one observed an effect at 400 ms post–picture onset, interpreted as being consistent with self-monitoring (Schuhmann et al., 2012). Note that these studies, while problematic for Indefrey and Levelt's account, likewise showed that earlier activation of posterior STG is not necessary for successful picture naming, as TMS did not produce an effect at 0, 100, or 200 ms (cf., Munding et al., 2016; Strijkers & Costa, 2016). Although it is tempting to conclude that word-form retrieval might occur later than estimated by both chronometric and electrophysiological methods, it is important to note that all three studies applied TMS solely to the left posterior STG (Brodmann area 22), whereas Indefrey and Levelt's meta-analysis attributed word-form processing to cortical tissue encompassing the posterior sections of *both* left MTG and STG. Schuhmann et al.'s (2012) study was the only one to apply TMS to the mid-portion of the MTG, finding an effect at 225 ms post–picture onset, consistent with Indefrey and Levelt's attribution of lexical-semantic processing. Consequently, mid- and posterior sections of MTG should be targets for future TMS investigations concerning the time course of production.

Alternatively, Indefrey and Levelt's attribution of posterior MTG/STG might be wrong, and a different region could subserve phonological word form retrieval. For example, using lesion-symptom mapping (LSM; see Wilson, Chapter 2 in this volume), Schwartz, Faseyitan, Kim, & Coslett (2012) and Dell, Schwartz, Nozari, Faseyitan, & Coslett (2013) analyzed speech error data from large cohorts of aphasic patients and implicated a region *adjacent* to Wernicke's area, the left inferior parietal lobe (IPL, comprising supramarginal and angular gyri, and planum temporale), in phonological/phonemic errors during picture naming. They interpreted their findings as consistent with a dorsal stream, articulatory-based account of phonological processing in production (see also Hickok, Chapter 20 in this volume). However, a reanalysis of Schwartz et al.'s (2012) data examining phonological neighborhood density effects (as lexical phonological processing involves activating not only the target word, but also phonologically related words) implicated both posterior STG and IPL (Mirman & Graziano, 2013). Both regions were also reported in a sparse-design fMRI study of phonological neighborhood effects in production (Peramunage, Blumstein, Myers, Goldrick, &

Baese-Berk, 2011). Of note, other lesion symptom mapping studies have reported left posterior MTG/STG rather than IPL, consistent with Indefrey and Levelt's account (e.g., Butler, Lambon Ralph, & Woollams, 2014). Future investigations using more fine-grained analyses of aphasics' speech errors differentiating lexical versus post-lexical phonological representations are needed (see Goldrick & Rapp, 2007; e.g., Schwartz et al., 2012 analyzed *all* nonword errors, regardless of their phonological overlap with the target).

Investigating the Spatiotemporal Components of Speech Production Models with Psycholinguistic Paradigms

In this next section, we summarize and discuss some key findings from neurolinguistic investigations using context manipulations in picture-naming paradigms to characterize processing stages in speech production. As the spatiotemporal components corresponding to representational stages in production models are relatively well delineated (see earlier discussion), neurolinguistic investigations are informative for testing rival accounts that attribute manipulations of an experimental factor to different processing stages (see de Zubicaray, 2012). However, context manipulations influencing the time course of production in chronometric studies likewise influence the timing of evoked responses in electrophysiological recordings, so should not be used for estimating temporal signatures of specific processing stages during simple production tasks (see Piai, Roelofs, Jensen, Schoffelen, & Bonnefond, 2014; cf. Munding et al., 2016). Rather, they are useful for demonstrating the correlates of the cognitive effect of interest. Here, we constrain our review to paradigms and context effects for which results from multiple sources of evidence are available, that is, across functional neuroimaging, electrophysiological, lesion-mapping, and/or brain simulation methods. We interpret only reliably reported findings across multiple studies.

Picture-Word Interference

Over four decades, the picture-word interference (PWI) paradigm has been used to test hypotheses about processing stages involved in spoken-word production (Rosinski, Golinkoff, & Kukish, 1975). In brief, the PWI paradigm involves participants naming a set of target pictures in context with written or auditorily presented distractor words. The most commonly employed manipulations in neurolinguistic studies involve distractors either semantically or phonologically related to the target picture name, compared with unrelated words. The *semantic interference* effect refers to the finding that naming latencies are significantly slower for pictures paired with categorically related versus unrelated words (e.g., a pictured "cow" with related distractor "pig" versus unrelated distractor "pin"). Conversely, phonologically related distractors (i.e., showing phoneme overlap with the picture name, e.g., a pictured "cow" with related distractor "couch") have been shown to facilitate (speed) target naming compared to unrelated distractors (e.g., "pin"). Both effects occur reliably within a small range of distractor stimulus onset asynchronies (SOAs) around target picture presentation (–150 to 150 ms; i.e., the distractor word is presented up to 150 ms before the picture or after picture presentation), with simultaneous distractor-target presentation usually employed. Virtually all production accounts attribute the locus of the phonological facilitation effect to the word form retrieval stage of processing. However, the locus of the semantic interference effect is a matter of debate between rival accounts. According to the lexical-selection-by-competition account, lemmas compete for selection and semantically related distractors increase this competition, delaying the selection process, which surfaces as longer naming latencies for the related condition (e.g., Piai et al., 2014). Conversely, according to post-lexical accounts, the semantic interference effect emerges in later stages, closer to articulation onset (see Mahon, Costa, Peterson, Vargas, & Caramazza, 2007). In addition, recent accounts have increasingly proposed involvement of top-down selection and control processes for resolving competition among lexical candidates.

Our review identified over 20 neurolinguistic studies of semantic interference and phonological facilitation using the PWI paradigm with EEG, MEG, fMRI, transcranial direct current stimulation (tDCS), and lesion patients. Of note, there is considerable variability in experimental designs across studies, including departures from the standard PWI procedure. A critical design feature of the PWI paradigm is that the same set of target pictures is used in each condition, with each picture paired with a different distractor word, ensuring that target processing is identical. Distractors are matched on a range of lexical variables, and the same words are often re-paired with different pictures to create the unrelated condition. Distractors may also be target picture names (i.e., members of the response set). Some studies include another condition, for example, picture naming in the absence of a distractor, or the picture name itself, or a neutral distractor condition (e.g., a row of Xs, nonwords, or symbols). Here, we restrict our review to canonical (i.e., related versus unrelated) contrasts for the semantic interference and phonological facilitation effects of interest. For both effects, we report differential activity associated with related compared to unrelated distractors (i.e., mean activity increases for related versus unrelated distractors, and vice versa).

Seven fMRI studies, two lesion studies, one tDCS study, and one MEG study have provided spatial location/source information for the semantic interference effect, all of which (except two) employed written distractors (Abel et al., 2009; Abel, Dressel, Weiller, & Huber, 2012; de Zubicaray & McMahon, 2009). Of the fMRI studies, four departed from the traditional PWI design by using unique sets of target pictures per distractor condition, or a distractor SOA of 550 ms (i.e., distractor presented after picture onset), and all used continuous rather than optimal sparse imaging designs (Abel et al., 2009; Abel et al., 2012; Diaz et al., 2014; Rizio, Moyer, & Diaz, 2017; Spalek & Thompson-Schill, 2008). Diaz et al. (2014) failed to observe any significant activity for the contrast of related versus unrelated distractor conditions in either whole brain or Region of interest (ROI) analyses. Abel et al.'s (2012) reanalysis of their 2009 study data reported significantly increased activity in the left IFG and reduced activity in left lingual and bilateral precentral gyri, left ACC, posterior STG, parietal operculum, and bilateral cuneus. Conversely, Rizio et al. (2017) observed only significantly increased activity in the bilateral middle frontal gyrus (MFG), bilateral MTG, and precuneus. Spalek and Thompson-Schill (2008) did not observe a significant semantic interference effect in naming latencies (likely due to the late SOA employed), and reported increased blood oxygenation level dependent (BOLD) signal in the right posterior cerebellum and left fusiform and parahippocampal gyri. The inconsistent results across the four studies might therefore reflect the use of unique picture sets in each condition, written versus auditory distractors, a late distractor SOA, speech-related artifacts in continuous imaging, or a combination of all these issues.

More consistent findings are provided by the one sparse and one continuous event-related fMRI study and one MEG study using the standard PWI design with written distractors (de Zubicaray, Hansen, & McMahon, 2013; Piai, Roelofs, Acheson, & Takashima, 2013, Piai et al., 2014). A consistent finding across all studies is *reduced* activity in left mid- to posterior MTG and STG for related versus unrelated distractors. This pattern was also found in another sparse design fMRI study using auditory distractors (de Zubicaray & McMahon, 2009). Piai and Knight (2018; see also Piai, Riès, & Swick, 2016) also reported increased semantic interference in error rates for patients with left lateral temporal cortex lesions, but not for patients with IFG lesions. However, Henseler, Mädebach, Kotz, and Jescheniak (2014) failed to observe any modulation of semantic interference with tDCS applied to the left posterior MTG or IFG. Notably, across studies, semantic interference was not consistently associated with involvement of cortical regions attributed to post-lexical processes or mechanisms proposed for resolving competition among semantic competitors (e.g., premotor cortex or IFG). Thus, the available data support a lexical-level rather than post-lexical account of semantic interference in PWI (cf., Mahon et al., 2007).

Of the six EEG studies and one MEG study attempting to characterize event-related responses (i.e., event-related potentials [ERPs] and event-related fields [ERFs]) to semantic interference using stimulus-locked analyses, one departed from the typical PWI design by blocking (and cycling) category members (Aristei, Melinger, & Abdel Rahman, 2011), while two others failed to observe any significant differences between related and unrelated ERPs (Hirschfeld, Jansma, Bölte, & Zwitserlood, 2008; Piai, Roelofs, & van der Meij, 2012). Across the remaining four studies, semantic interference consistently modulated the event-related responses in the N400 time window (around 250–550 ms), showing a more negative-going waveform or smaller amplitude for related compared to unrelated distractors (i.e., N200–400; Blackford, Holcomb, Grainger, & Kuperberg, 2012; Dell'Acqua et al., 2010; Piai et al., 2014; Zhu, Zhang, & Damian, 2016). Given the relatively longer naming latencies observed in PWI, the electrophysiological data are also consistent with a lexical-level account of the semantic interference effect.

Phonological facilitation in PWI has been investigated by five fMRI studies. Two of these used the standard paradigm, each with written and auditory distractors in sparse designs (de Zubicaray, McMahon, Eastburn, & Wilson, 2002; de Zubicaray & McMahon, 2009). Three further fMRI studies departed from the standard PWI design and used continuous imaging. Surprisingly, all three of these latter studies failed to observe significant differences in naming latencies; that is, the experimental manipulation did not produce the phonological facilitation effect of interest (Abel et al., 2009; Abel et al., 2012; Diaz et al., 2014; Rizio et al., 2017). This might reflect the use of unique picture sets or gradient noise associated with continuous imaging that prevents accurate measurements of response latency even with noise-canceling techniques (although Abel and colleagues also failed to observe a significant difference in an identical behavioral experiment conducted outside the scanner). Diaz et al. (2014) reported increased activation for phonologically related versus unrelated distractors in bilateral supramarginal and angular gyri, whereas Rizio et al. (2017) reported signal increases in the right angular gyrus and left superior parietal cortex, and Abel et al. reported increased activity in left supramarginal gyrus and inferior parietal lobule (BA 40), accompanied by signal reductions in bilateral visual cortex, left ACC, and parahippocampal gyrus. Ignoring the absence of evidence for a significant phonological effect in the behavioral data across studies, the fMRI data could be interpreted as reflecting relatively consistent involvement of the left IPL, which might be considered to support a dorsal stream, articulatory-based account of phonological processing in production (e.g., Dell et al., 2013; Schwartz et al., 2012; but see further discussion in this chapter).

Across the two fMRI studies using sparse event-related designs, BOLD signal decreases were observed consistently in the left posterior MTG/STG (de Zubicaray et al., 2002; de Zubicaray & McMahon, 2009). Additional evidence for left posterior temporal cortex involvement is provided by Pisoni and colleagues (Pisoni, Cerciello, Cattaneo, & Papagno, 2017), using anodal tDCS that significantly reduced the magnitude of the facilitation effect. The evidence for left IFG involvement is equivocal. Piai et al. (2016) reported an increased facilitation effect in left IFG lesion patients compared to healthy controls. Significantly reduced BOLD signal responses in left IFG were reported in one auditory PWI study (de Zubicaray & McMahon, 2009). However, another fMRI study did not observe differential left IFG activity for the phonological effect (de Zubicaray et al., 2002), and Pisoni et al. (2017) reported tDCS applied to left IFG did not influence the facilitation effect. Of the four EEG studies to investigate event-related responses to phonological facilitation in PWI, two failed to observe any significant differences in stimulus-locked waveforms (Blackford et al., 2012; Bürki, 2017), and the remaining two reported different results, ranging from a less negative-going waveform between 250 and 450 ms (Dell'Acqua et al., 2010) to a more positive-going waveform between 450 and 600 ms (Zhu et al. 2016; in Chinese).

Figure 19.1 provides a summary of the spatiotemporal components associated with the semantic (left) and phonological (right) effects in picture-word interference. Both

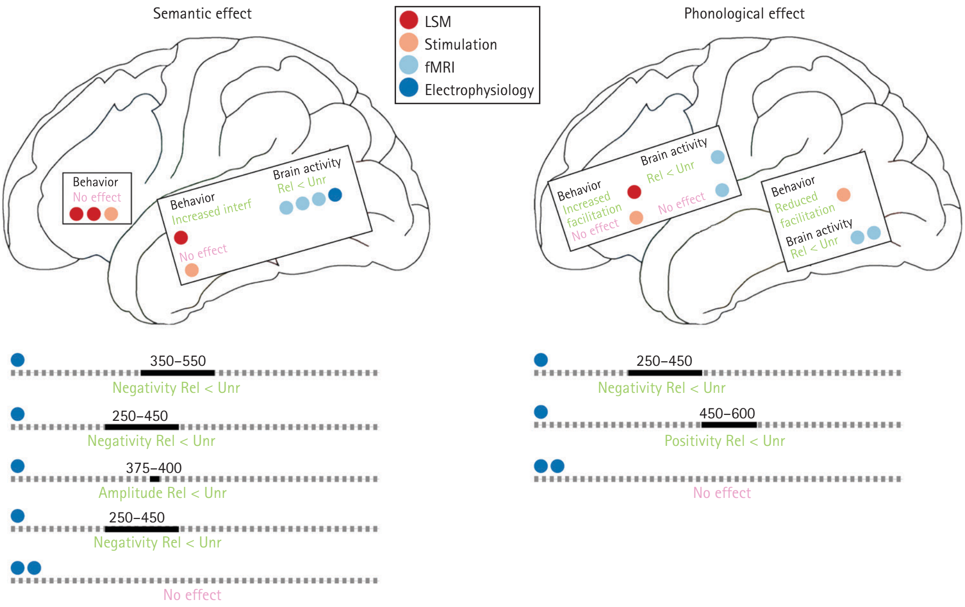
Semantic effect
LSM
Stimulation
fMRI
Electrophysiology
Phonological effect
Behavior
No effect
Behavior
Increased interf
No effect
Brain activity
Rel < Unr
Behavior
Increased facilitation
No effect
Brain activity
Rel < Unr
No effect
Behavior
Reduced facilitation
Brain activity
Rel < Unr
350–550
Negativity Rel < Unr
250–450
Negativity Rel < Unr
375–400
Amplitude Rel < Unr
250–450
Negativity Rel < Unr
No effect
250–450
Negativity Rel < Unr
450–600
Positivity Rel < Unr
No effect

FIGURE 19.1. Schematic view of the evidence on the spatial (for the left mid- to posterior superior and middle temporal gyri and left IFG) and temporal components of semantic and phonological context effects in picture-word interference. Only studies using the standard paradigm are shown. Each method is color coded (light blue: fMRI; dark blue: electrophysiology; red: lesion-symptom mapping, LSM; pink: noninvasive brain stimulation). Each colored circle represents one study.

Abbreviations: interf = interference; rel = related; unr = unrelated.

significant and nonsignificant effects are shown for studies using the standard paradigm. Each study is represented by a circle, which is color-coded according to the method employed. The most consistent pattern for the semantic effect seems to be decreased brain activity in the left posterior temporal lobe (i.e., related < unrelated), in a window ranging around 250–500 ms. For the phonological effect, decreased brain activity in the posterior temporal lobe seems to be the only reproducible pattern, although not as consistent as for the semantic effect.

Blocked Cyclic Naming

Another production paradigm with a relatively large neurolinguistic evidence base is blocked cyclic naming. The most frequently implemented version of the paradigm entails a small set of pictures that participants name repeatedly over several cycles, alternating between categorically related (e.g., animals) versus unrelated contexts (animals, musical instruments, vehicles, vegetables). Like the PWI paradigm, categorically related contexts elicit a semantic interference effect, typically observed only from the second cycle onward (for a review, see Belke & Stielow, 2013). Theoretical accounts have been devised to specifically explain semantic interference in this paradigm, with several incorporating evidence from lesion, neuroimaging, and noninvasive brain stimulation studies. All of these accounts propose roles for both the left posterior MTG/STG and left IFG, in lexical-semantic processing and various control/selection-biasing mechanisms, respectively (e.g., Belke & Stielow, 2013; Oppenheim, Dell, & Schwartz, 2010; Schnur et al., 2009). An incremental learning mechanism has also been proposed to be responsible for the persistence of interference across cycles but has received less research attention in terms of its neural correlates (Damian & Als, 2005; Oppenheim et al., 2010).

Neuroimaging, electrophysiological, brain stimulation, and LSM studies of semantic interference in blocked cyclic naming mostly provide evidence for involvement of left posterior MTG/STG. However, there is little consistency with respect to the direction of the effect across studies. Two early fMRI studies involved nonstandard design and analysis manipulations, making results difficult to interpret. For example, Hocking, McMahon, & de Zubicaray (2009) manipulated visual feature overlap across blocks and were unable to record naming latencies during perfusion fMRI, while Schnur et al. (2009) reported findings for a contrast of semantic interference versus phonological facilitation (i.e., [semantic > unrelated] > (phonological > unrelated]). Both studies reported signal increases. One perfusion fMRI experiment using the standard design reported signal reductions (de Zubicaray, Johnson, Howard, & McMahon, 2014). Two tDCS studies reported opposite effects for online and offline stimulation protocols (Meinzer, Yetim, McMahon, & de Zubicaray, 2016; Pisoni, Papagno, & Cattaneo, 2012). One LSM study reported a significant increase in error rates (Harvey & Schnur, 2015). Interestingly, the peak spatial coordinates reported by Harvey and Schnur's (2015) LSM and de Zubicaray et al.'s (2014) perfusion fMRI studies in posterior MTG/STG were virtually identical. An MEG study likewise reported differential MTG/STG activity (Maess, Friederici, Damian, Meyer, & Levelt, 2002; note the direction of the effect could not be interpreted given the principal component analysis approach). An intracranial EEG study reported decreases in the evoked responses in the MTG and STG, but increases in the inferior temporal lobe (Riès et al., 2017). Finally, a TMS study by Krieger-Redwood and Jefferies (2014) reported an effect of stimulation over posterior MTG/STG only in the first cycle of naming (i.e., prior to the emergence of the interference effect).

The evidence from a similar range of studies is mostly consistent with left IFG involvement, although there are some notable exceptions. Whereas only one of three fMRI studies reported significant IFG activity using a nonstandard comparison (Schnur et al., 2009; cf. Hocking et al., 2009; de Zubicaray et al., 2014), two of three studies of aphasics with IFG lesions noted significant effects in error rates (Riès, Greenhouse, Dronkers, Haaland, & Knight, 2014; Schnur et al., 2009; cf. Harvey & Schnur, 2015). Two of three tDCS studies reported an effect of stimulation to the left IFG, reducing the magnitude of the interference effect using offline (Pisoni et al., 2012) and online stimulation protocols (Meinzer et al., 2016; cf. Westwood, Olson, Miall, Nappo, & Romani, 2017), although one TMS study observed an effect only in the first cycle of naming (i.e., prior to semantic interference occurring; Krieger-Redwood & Jefferies, 2014). An additional tDCS study reported a significant reduction in the magnitude of semantic interference following online but not offline stimulation over the dorsal frontal cortex (Wirth et al., 2011).

Unfortunately, EEG and MEG estimates of stimulus-locked event-related responses for the semantic interference effect vary considerably, both in terms of timing and polarity of waveforms: from 150–225 ms (Maess et al., 2002), 200–500 ms (Wang, Shao, Chen & Schiller, 2017; smaller negativity; in Chinese), 220–450 ms (Janssen, Carreiras, & Barber, 2011; smaller negativity), 270–315 ms (Python, Farghier, & Laganaro, 2017; smaller positivity), to 500–750 ms (Janssen, Hernández-Cabrera, van der Meij, & Barber, 2015; smaller positivity). Two other electrophysiological studies either used a nonstandard design combining PWI and blocking (Aristei et al., 2011) or failed to observe any significant differences in event-related responses (Llorens, Trebuchon, Riès, Alario, & Liegeois-Chauvel, 2014). The considerable variability in analysis techniques across studies might explain the inconsistent findings, as might the authors' choice of interpretations for event-related responses in particular time windows. With respect to the latter, some studies reported more than one time window for event-related responses, permitting some flexibility in interpretation. For example, Maess et al. (2002) reported a second evoked response around 450–475 ms interpreted as self-monitoring, whereas Janssen et al. (2015) reported an effect in an earlier 250–400 ms time window, which they interpreted in terms of conceptual processing.

Substantial evidence in animals and humans implicates the hippocampus in both implicit (unconscious) and explicit retrieval of relational information (see Duss et al., 2014; for review, see Henke, 2010), making it a plausible candidate for the implicit incremental learning mechanism proposed in psycholinguistic accounts of semantic interference in blocked cyclic naming (e.g., Damian & Als, 2005; Oppenheim et al., 2010). One perfusion fMRI study and one intracranial EEG study explicitly targeted hippocampal activity using the standard design, interpreting their findings as reflecting the operation of an incremental learning mechanism (de Zubicaray et al., 2014; Llorens, Dubarry, Trébuchon, Chauvel, Alario, & Liégeois-Chauvel, 2016). The perfusion fMRI study revealed a reduction in activity during the related context. Using intracranial electrodes implanted directly in bilateral hippocampus, Llorens et al. (2016) reported that the amplitude of the event-related responses (a negativity peaking around 600 ms) in the related blocks was smaller than in unrelated blocks. Crucially, this negative peak emerged progressively from the second cycle of naming onward.

Figure 19.2 provides a summary of the spatiotemporal components associated with the semantic effect in blocked cyclic naming. Both significant and nonsignificant effects are shown for the studies using the standard paradigm. Each study is represented by a circle, color-coded according to the method employed. The most consistent pattern for the semantic effect seems to be an impact on the magnitude of the interference depending on whether the left IFG is stimulated noninvasively or is damaged. Decreased brain activity in the left posterior temporal lobe (i.e., related < unrelated) is also relatively consistent, and again brain stimulation or damage in that area impact the magnitude of the interference effect. Regarding the temporal component, modulations in the 200–450 ms range seem to be the most consistent pattern, with the homogeneous condition showing

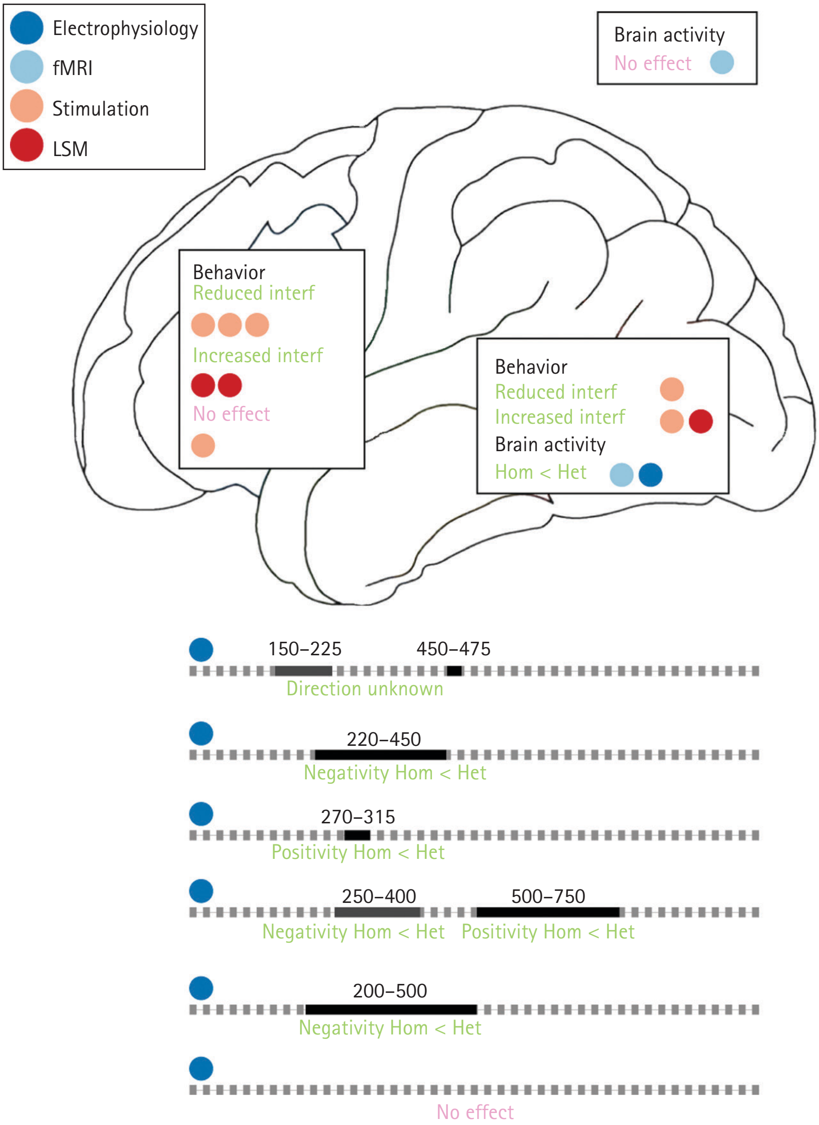
Electrophysiology
fMRI
Stimulation
LSM
Brain activity
No effect
Behavior
Reduced interf
Increased interf
No effect
Behavior
Reduced interf
Increased interf
Brain activity
Hom < Het
150–225
450–475
Direction unknown
220–450
Negativity Hom < Het
270–315
Positivity Hom < Het
250–400
500–750
Negativity Hom < Het
Positivity Hom < Het
200–500
Negativity Hom < Het
No effect

FIGURE 19.2. Schematic view of the evidence on the spatial (for the left superior and middle temporal gyri and left IFG) and temporal components of the semantic context effect in blocked cyclic naming. Only studies using the standard paradigm are shown. Each method is color-coded (light blue: fMRI; dark blue: electrophysiology; red: lesion-symptom mapping, LSM; pink: non-invasive brain stimulation). Each colored circle represents one study.

Abbreviations: het = heterogeneous; hom = homogeneous; interf = interference.

decreased amplitude relative to the heterogeneous condition, although as noted earlier, authors tend to disagree on the interpretation of that modulation.

Continuous Naming

The continuous-naming paradigm introduced by Howard, Nickels, Coltheart, & Cole-Virtue (2006) requires participants to name a pseudo-random series of pictures, and likewise elicits a semantic interference effect. Within the series, exemplars from a range of semantic categories are interspersed with filler items. The interval or lag between each consecutive category exemplar is also varied. Semantic interference in this paradigm manifests from the second ordinal position within a category and accumulates linearly at ~30 ms for each successive categorically related picture. As with the semantic interference effects in PWI and blocked cyclic naming tasks, the left lateral temporal lobe is proposed to play a prominent role in lexical-semantic retrieval in continuous naming (e.g., Belke, 2013). These accounts also tentatively ascribe a role for the left IFG in either top-down, selection-biasing, or activation-boosting mechanisms (Belke, 2013; Canini et al., 2016; Oppenheim et al., 2010). Further, at least one account presumes that semantic interference in the continuous and blocked cyclic naming arises due to a common mechanism(s) (Oppenheim et al., 2010), leading to the expectation that the spatiotemporal mechanisms will bear at least a strong resemblance across paradigms. A cumulative interference effect for phonologically related words has also been reported in continuous reading aloud (Mulatti, Peresotti, Job, Saunders, & Coltheart, 2012), but is yet to be subjected to neurolinguistic investigation.

Despite being introduced only a decade earlier, the continuous-naming paradigm has been the subject of three fMRI studies, as many EEG studies, one lesion study, and one tDCS investigation. Of the three fMRI studies, two employed continuous BOLD acquisitions (Canini et al., 2016; Wilson, Isenberg, & Hickok, 2009), while the third used perfusion imaging (de Zubicaray, McMahon, & Howard, 2015). Wilson et al. (2009) employed Howard et al.'s (2006) stimuli, yet were unable to detect any significant BOLD signal correlates of cumulative interference. Canini et al.'s (2016) design departed from Howard et al.'s by presenting participants with two different experimental lists, averaging the ordinal position data. They were unable to report naming latency data due to the gradient noise accompanying continuous imaging, and did not find evidence for cumulative interference in error rates. Their parametric fMRI analysis revealed a linear increase in BOLD signal in the left IFG and caudate. However, this analysis included the first ordinal position data, whereas the cumulative effect is calculated from the second ordinal position onward. Using perfusion imaging with the original Howard et al. experimental lists, de Zubicaray et al. (2015) reported a significant linear increase in left mid-MTG and perirhinal cortex activity from the second ordinal position onward. However, Westwood et al. (2017) reported that tDCS to left posterior MTG did not modulate the interference effect compared to sham (but see Gauvin, Meinzer, & de Zubicaray, 2017, for a critique of Westwood et al.'s methods). Thus, the evidence for left lateral temporal lobe involvement in cumulative semantic interference is best described as inconsistent and in need of further investigation.

The findings from lesion, EEG, and tDCS studies are more consistent with respect to the left IFG. Riès, Karzmark, Navarrete, Dronkers, & Knight (2015) failed to observe an effect of left IFG lesions on cumulative interference in either naming latencies or error rates. Westwood et al. (2017) reported that tDCS to left IFG did not modulate the interference effect compared to sham (but see Gauvin et al., 2017). Using a nonstandard design omitting the lag manipulation, one study failed to observe any differences associated with cumulative interference (Llorens et al., 2014). Both Costa et al. (2009) and Rose and Abdel Rahman (2016) reported a linear modulation of positive waveforms at around 200–400 ms post–picture onset over only posterior electrodes, in addition to significant correlations with naming latencies between 208 and 388 ms, and 268 and 413 ms, respectively, noting that their findings were broadly consistent with the time window suggested for lexical selection (see spatial and temporal components section earlier in this chapter).

Figure 19.3 provides a summary of the spatiotemporal components associated with the cumulative semantic effect in continuous naming. Both significant and nonsignificant effects are shown for the studies using the standard paradigm. Each study is represented by a circle, color-coded according to the method employed. The paucity of studies contributes to an impression of a lack of consistency in findings. In the temporal domain, a linear modulation of positive-going waveforms in the 250–400 range seems to be the consistent finding over two studies.

ARE TOP-DOWN CONTROL/SELECTION BIASING MECHANISMS REALLY REQUIRED TO RESOLVE SEMANTIC INTERFERENCE?

Our review of findings from the PWI, blocked cyclic, and continuous-naming paradigms is informative both from a neurolinguistic perspective and for constraining cognitive accounts of production. All three paradigms were designed to promote activation of multiple lexical candidates, and observations of behavioral semantic interference effects across paradigms are typically interpreted in terms of common mechanisms. Recent psycholinguistic accounts of all three paradigms have begun to incorporate neural data, with a particular emphasis on intervention by domain-general, top-down cognitive control mechanisms to resolve competition during production. For the most part, these accounts have proposed a prominent role for the left IFG in resolving competition among lexical-semantic competitors. Indeed, Belke and Stielow (2013) concluded, “It appears that any future model of word production unavoidably faces the challenge of specifying how left frontal mechanisms of domain-general cognitive control interact

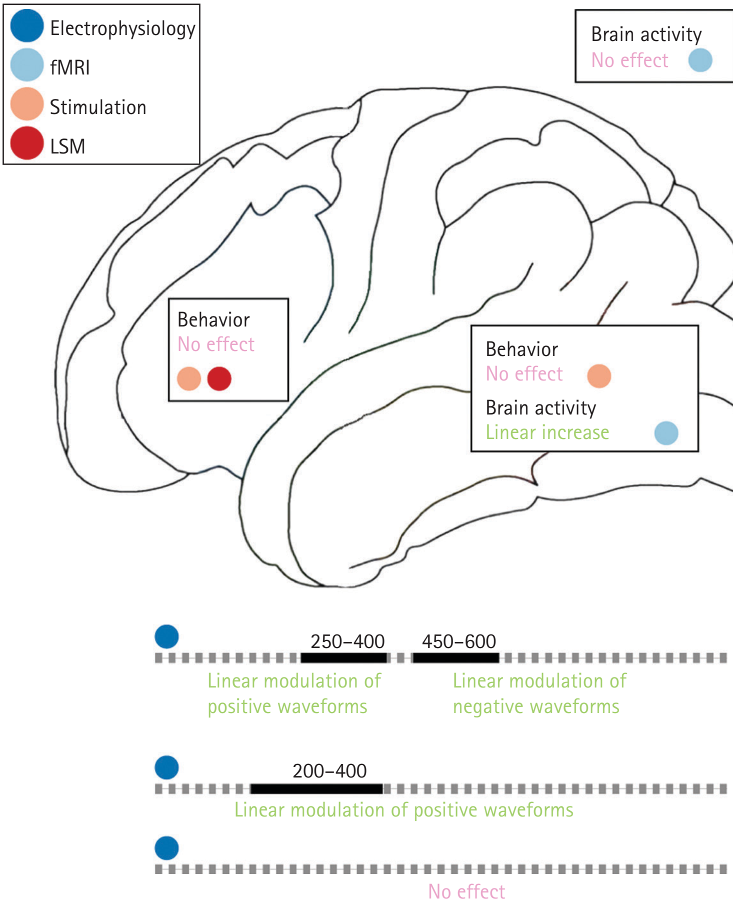
Electrophysiology
fMRI
Stimulation
LSM
Brain activity
No effect
Behavior
No effect
Behavior
No effect
Brain activity
Linear increase
250–400
450–600
Linear modulation of positive waveforms
Linear modulation of negative waveforms
200–400
Linear modulation of positive waveforms
No effect

FIGURE 19.3. Schematic view of the evidence on the spatial (for the left MTG and left IFG) and temporal components of the cumulative semantic effect in continuous naming. Only studies using the standard paradigm are shown. Each method is color-coded (light blue: fMRI; dark blue: electrophysiology; red: lesion-symptom mapping, LSM; pink: noninvasive brain stimulation). Each colored circle represents one study.

with paradigmatic interference during lexical-semantic encoding" (p. 23). Based upon the evidence we have reviewed here, this conclusion appears to be a significant overstatement.

We could find no reliable evidence for a role of the left IFG in semantic interference in either PWI or continuous-naming paradigms. Although absence of evidence might not be evidence of absence, the fact that left IFG involvement was observed only semi-reliably in blocked cyclic naming studies of semantic interference suggests the need for a reassessment of proposals concerning the ubiquitous involvement of domain-general, top-down mechanisms in biasing or resolving competition during spoken word production (subserved by the left IFG). At the very least, it demonstrates that semantic interference across the three naming paradigms does not necessarily reflect identical mechanisms (cf. Oppenheim et al., 2010). Of the three paradigms, blocked cyclic naming is the least akin to naturalistic speech, involving the massed repetition/cycling of a small set of responses. The prominence afforded to this paradigm in speech production accounts is therefore questionable. It is also worth emphasizing that semantic interference effects may not necessarily reflect lexical-level processes either. In other naming paradigms, semantic interference has been attributed to prelexical, conceptual processes, for example, post-cue naming (Dean, Bub, & Masson, 2001; Hocking, McMahon, & de Zubicaray, 2010) and negative priming (de Zubicaray, McMahon, Eastburn, Pringle, & Lorenz, 2006; Tipper, 1985).

As we have noted, proposals for top-down involvement have now extended to simple production tasks such as basic picture naming (e.g., Munding et al., 2016; Strijkers & Costa, 2016). Such proposals require theoretical motivation beyond the mere observation of neurophysiological responses. For example, when speakers can produce two to four words per second, and produce errors no more than one to two times every 1,000 words during everyday speaking (Levelt, Roelofs, & Meyer, 1999), it would be useful to explain precisely why top-down intervention in selecting lexical candidates for production is so essential.

This is not to say that there is no evidence of left IFG or other control-related mechanisms in the studies we reviewed. In neuroimaging studies of the PWI paradigm, lateral and medial frontal (ACC or SMA) engagement was reported relatively consistently for contrasts of related versus identity or neutral conditions (de Zubicaray, Wilson, McMahon, & Muthiah, 2001; Piai et al., 2013; Piai et al., 2014), and patients with left IFG lesions similarly showed increased interference for the contrast of a lexical distractor versus a neutral condition when compared to healthy controls (Piai et al., 2016). This suggests a role for the left IFG in resolving competition introduced by competing *linguistic* information, rather than selecting among semantic competitors per se. This may reflect the operation of an early attention-blocking mechanism, as Piai et al. (2016) suggested.

A View to the Future

In this chapter, we have examined a number of issues facing researchers when investigating the spatiotemporal components of speech production. A relatively clear impression from our review is that suboptimal methods have compromised a significant proportion of studies. Inconsistencies in BOLD fMRI study results were a regular outcome with standard continuous imaging acquisitions. We recommend that continuous BOLD acquisitions be avoided in future fMRI studies of speech production. As neuroimaging is an expensive enterprise, adherence to methodological best practice is both a scientific and economic imperative. Similarly, findings from electrophysiological recordings showed such variability that they were uninterpretable for some psycholinguistic effects. A consensus approach to design and analysis with these techniques is sorely needed. Nonstandard experimental designs were also frequently a source of problems for interpretation. Throughout our review, we relied on converging evidence from multiple sources of data to support our interpretations. Perhaps the only relatively consistent finding across paradigms was for the 250–450 ms time window and posterior temporal lobe (MTG/STG) involvement. Notably, many arguments that engendered debate in the literature emphasized data from a single modality—proposals concerning evidence for parallel rather than serial activation of processing stages being a prominent example.

We reviewed findings from context manipulations in picture-naming paradigms, as these reflect the most well-developed evidence base for investigating the spatial and temporal components of processing stages in spoken-word production, and in particular the stage of retrieving words from the mental lexicon. The neurolinguistic literature currently reflects only a fraction of the context manipulations conducted in psycholinguistic studies, and is strongly biased toward semantics and monolingual production. This imbalance needs to be addressed. Outside of Stroop-like color-naming paradigms that have been the topic of many reviews, there is a paucity of neurolinguistic evidence concerning context manipulations in reading aloud. Recent sparse and perfusion fMRI studies have successfully mapped the networks involved in sentence production (e.g., Geranmayeh, Wise, Mehta, & Leech, 2014; Kemeny, Ye, Birn, & Braun, 2005; Tremblay & Small, 2011), paving the way for more sophisticated manipulations. Finally, compared to the psycholinguistic literature, neurolinguistic studies of self-monitoring mechanisms are also scarce, and there is a clear tension between domain-general and speech-perception-based accounts that should prove a fruitful area for inquiry.

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CHAPTER 20

THE DORSAL STREAM AUDITORY-MOTOR INTERFACE FOR SPEECH

GREGORY HICKOK

As the title forecasts, this chapter is about the dorsal auditory-motor speech interface. This network is part of a larger system involved in auditory, speech, and language processing that is roughly organized into two main streams, referred to as the dorsal and ventral streams, corresponding to their locations on the lateral cortex. We review the organization of the broader dual-stream context, including its historical foundation. We then turn to recent progress in mapping the dorsal stream and understanding its computational basis. A current hypothesis is that the dual stream supports speech production via a feedback-control mechanism. This line of investigation offers the hope of integrating psycholinguistic, neurolinguistic, and motor control research.

Dual-Stream Models: A Computational Necessity

The brain must perform at least two tasks with incoming sensory information: (1) map it onto conceptual representations for the purpose of recognizing what is being perceived, and (2) map it onto motor representations for the purpose of generating an appropriate action in response to the information. This makes intuitive sense for visual perception, where, for example, one needs to recognize what an object is and how to use information about size, shape, orientation, and distance to control a limb for reaching and grasping the object (Milner & Goodale, 1995). In the case of speech, these two kinds of mappings are equally necessary, which led to the development of the dual-stream model of speech processing (Hickok & Poeppel, 2000, 2004, 2007) (Figure 20.1). For example, one needs to be able to recognize what words are being spoken, and one needs to be

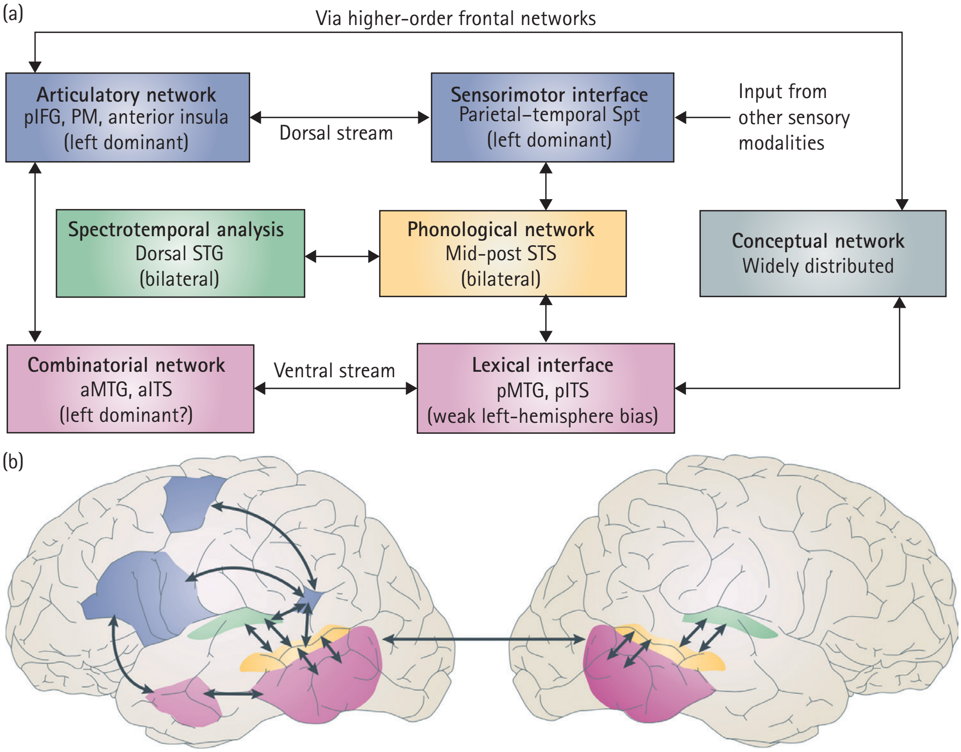
(a)
Via higher-order frontal networks
Articulatory network
pIFG, PM, anterior insula
(left dominant)
Dorsal stream
Sensorimotor interface
Parietal–temporal Spt
(left dominant)
Input from
other sensory
modalities
Spectrotemporal analysis
Dorsal STG
(bilateral)
Phonological network
Mid-post STS
(bilateral)
Conceptual network
Widely distributed
Combinatorial network
aMTG, aITS
(left dominant?)
Ventral stream
Lexical interface
pMTG, pITS
(weak left-hemisphere bias)
(b)

FIGURE 20.1. (A) Schematic diagram of the dual-stream model. Phonological network diverges into two streams: a dorsal sensorimotor stream supporting speech motor control and a ventral sensory-conceptual stream supporting comprehension. The relation between auditory-phonological and articulatory representations, on one hand, and auditory-phonological and conceptual representations, on the other, is mediated by distinct interface systems, the "sensorimotor interface" and the "lexical interface." (B) Approximate anatomical locations of the dual-stream model components. Regions shaded pink represent the more bilaterally organized ventral stream. Regions shaded blue represent the dorsal stream, which is strongly left dominant. Functional area Spt (Sylvian parietal temporal) is the posterior-most blue shaded area.

pIFG, posterior inferior frontal gyrus; PM, premotor; Spt, Sylvian parietal-temporal; STG, superior temporal gyrus; STS, superior temporal sulcus; aMTG; anterior middle temporal gyrus; aITS, anterior inferior temporal sulcus; pMTG, posterior middle temporal gyrus; pITS, posterior inferior temporal sulcus.

able to reproduce the words (and sentence patterns, etc.) of the language with one's own speech articulatory system.

The need to be able to reproduce perceived speech is most obvious in development, where the young child must perceive the sound patterns in the surrounding linguistic environment and learn to reproduce those patterns him- or herself (Doupe & Kuhl, 1999). But much evidence has shown that acoustic input plays a critical role in several aspects of speech production throughout life, including maintenance and fine-tuning of articulatory patterns (Waldstein, 1989), compensating for changing vocal tract state or environmental perturbations either experimentally (Houde & Jordan, 1998; Larson, Burnett, Bauer, Kiran, & Hain, 2001; Perkell, 2012) or in natural situations, such as talking with food the mouth, and in speech motor planning (Hickok, 2012; Hickok, Houde, & Rong, 2011; Houde & Nagarajan, 2011), as we will see in the following sections. Given that sensory information must be interfaced with conceptual systems, on one hand, and motor systems, on the other, and given that these are largely distinct computational tasks, it is no surprise that dual-stream models have been proposed in all the major sensory modalities and have been proposed repeatedly over the last century and a half (Dijkerman & de Haan, 2007; Hickok & Poeppel, 2004; Ingle, 1973; Milner & Goodale, 1995; Poljak, 1926; Rauschecker & Scott, 2009; Wernicke, [1874] 1969).

DUAL-STREAM MODELS: HISTORICAL CONTEXT

Although most students and practitioners of cognitive neuroscience today trace the roots of dual-stream processing models to the pioneering work of Ungerleider and Mishkin and their "two visual system" proposal—the *what* versus *where* distinction (Ungerleider & Mishkin, 1982)—the idea was far from new. More than a century before Ungerleider and Mishkin's influential paper, Wernicke proposed a similar functional distinction for language: one stream that associates sound with concepts and another that associates sound with the motor speech system. And it wasn't just the language scientists who were on to the idea in the nineteenth century. Research coming out of Wilhelm Wundt's lab in the 1880s clearly makes a distinction between "apperception," the conscious recognition of the stimulus, and the ability of a stimulus to trigger a motor response more directly (discussed in Neumann, 1990). Ludwig Lange, for example, distinguished between muscular and sensorial reaction time in 1888, and Hugo Munsterberg underlined this perspective, stating,

> When we apperceive the stimulus, we have as a rule already started responding to it. Our motor apparatus does not wait for our conscious awareness, but does restlessly its duty, and our consciousness watches it and has no right to give it orders. (Munsterberg, 1889, p. 173, cited and translated by Neumann, 1990)

Twentieth-century research on the visual systems of frogs (Ingle, 1973), rodents (Schneider, 1969), and primates (Trevarthen, 1968) prior to Ungerleider and Mishkin's work also led to the conclusion that the visual system is split into two parallel streams. And, as we will see, Poljak concluded in a 1926 publication that the *auditory* system has a "double function."

The take-home message here is that the concept of dual processing streams has been arrived at from multiple perspectives (neuropsychology, psychophysics, neuroimaging), in multiple domains (notably language, vision, and audition), and repeatedly throughout the course of history. This suggests that there is an important generalization here. In fact, it has been suggested to be a fundamental principle of the cortical organization of sensory systems (Hickok & Poeppel, 2007), presumably due to the computational necessity of the distinct mapping functions.

We turn next to more specific dual-stream models in vision and audition.

Dual Streams in Vision

As noted earlier, the idea that the visual system is computationally bifurcated was well established by the time Ungerleider and Mishkin published their hugely influential chapter on the "Two Cortical Visual Systems" in 1982. They write,

> It has been our working hypothesis (Mishkin 1972; Pohl 1973) that the ventral or occipitotemporal pathway is specialized for object perception (identifying *what* an object is) whereas the dorsal or occipitoparietal pathway is specialized for spatial perception (locating *where* an object is). This distinction between the two types of visual perception is not new (see, for example, Ingle 1967; Held 1968). (Ungerleider & Mishkin, 1982, p. 549)

What the 1982 paper did was make the case that the two streams in the macaque monkey were entirely cortical, that their origin was the striate visual cortex. There were two basic observations: first, that damage to ventral temporal regions resulted in deficits in using object identity to perform a task, whereas damage to parietal regions resulted in deficits in using spatial cues to perform a task (Pohl, 1973); and second, that lesions of striate cortex interacted with the temporal and parietal lesions, thus pointing to the source of information flowing into the two streams (Ungerleider & Mishkin, 1982). It was noted by Ungerleider and Mishkin that spatial discrimination was not the only symptom observed in monkeys with parietal lesions; they also exhibited misreaching deficits, along with other classic parietal symptoms such as contralateral neglect and tactile discrimination. But it took another decade for the action-related deficits to surpass the spatial deficits in theoretical prominence in the form of Milner and Goodale's reformulation of the functional role of the dorsal stream into a "how" (sensorimotor) stream (Milner & Goodale, 1995; see also Neumann, 1990, who proposed a similar subdivision).

Evidence for the existence of *what* (recognition) versus *how* (sensorimotor) dual-processing streams in vision comes from a variety of sources. Milner and Goodale's book is still a nice review of much of the foundational data (Milner & Goodale, 1995). Some of the strongest arguments come from neuropsychology, where double dissociations can be found. Patients with visual form agnosia have severe deficits in recognizing objects by sight (tactile and auditory recognition is intact), yet are still able to interact with objects motorically in an appropriate way. A dramatic, and now famous case, patient D. F., was reported by Milner and colleagues, which clearly illustrates the dissociation (Milner et al., 1991; see Karnath, Ruter, Mandler, & Himmelbach, 2009, for recent brief review).

D. F. was unable to consciously indicate the orientation of a slot, but was able to "post" a card accurately through that same slot. Patients with visual form agnosia have ventral occipito-temporal lobe damage consistent with the ventral stream claim. However, most cases suffered brain damage due to carbon monoxide intoxication, which produces diffuse damage, and this has raised concerns regarding the underlying neuroanatomy (Karnath et al., 2009). But the functional dissociations remain clear, and a recent case of a stroke patient with focal ventral temporal lesions has been reported who exhibits the same pattern of dissociation (Karnath et al., 2009).

In contrast to visual agnosics, patients with optic ataxia are able to recognize objects by sight but have substantial difficulty in generating accurate reaching for and grasping of objects. They tend to grope for their targets instead of using visual guidance to determine trajectory and anticipatory grasp shaping of the hand. Lesions associated with optic ataxia have a posterior parietal lobe focus, consistent with the dorsal stream claim (Perenin & Vighetto, 1988).

The deficit in optic ataxia is not absolute, however. It mostly emerges when reaching for objects in the visual periphery, or when the reach requires rapid adjustments due to changing conditions, or when the object is unfamiliar (Rossetti, Pisella, & Vighetto, 2003)—precisely those conditions when the particulars of the object, as opposed to the *what* of the object, are critical for guiding action. This is an important point that has led to some confusion in the literature and is worth spending a few lines on here. If asked to demonstrate how to reach for a cup, one could do it in a fairly generic way. Most likely, the reach would extend straight out in front, at an average height of a table and with an average grip aperture. Presumably, we have a stored motor program for how to reach for the average cup in its average location, and no visual information is needed to do this. In a real reaching situation, where objects may not be of average size and in average locations, one will have to modify the default reach, and for that one needs visual input. Likewise, if a perturbation is introduced during the reach, a modification from the generic plan is required. These are the conditions that require analysis of visual details about the particular shape and location of the object, as opposed to invariant object properties, and these are the conditions that are most impaired in optic ataxia. The point is that even though reaching deficits only show up under some conditions, this does not dispute the existence of a sensorimotor system that is computationally tuned to guide reaching as opposed to object recognition.

Additional evidence for a dual-stream model in vision comes from behavioral experiments where it has been shown that psychophysical functions differ for action- versus non-action perceptual tasks. One controversial demonstration is that the Ebbinghaus illusion—object size perception that is dependent upon the size of surrounding objects—does not fool the visuomotor system, or at least does not fool it to the same degree (Aglioti, DeSouza, & Goodale, 1995; Haffenden & Goodale, 1998).

The illusion-based findings have been critiqued quite heavily and remain controversial (Franz & Gegenfurtner, 2008; Westwood & Goodale, 2011), but similar effects have been reported in other psychophysical paradigms (for review, see Westwood &

Goodale, 2011), and thus behavioral data are, on balance, consistent with findings from neuropsychology.

Dual Streams in Audition

Josef Rauschecker is often credited with idea that auditory cortex is functionally subdivided into two processing streams, a dorsal "where" stream and a ventral "what" stream (Rauschecker, 1998; Rauschecker & Scott, 2009), similar to previous claims in the primate visual system (Ungerleider & Mishkin, 1982). However, the idea of dual auditory streams predates Rauschecker's influential papers by several decades. Deutsch and Roll proposed separate "what" and "where" mechanisms for hearing in their 1976 report (Deutsch & Roll, 1976), citing then recent animal neurophysiological evidence for the distinction (Evans & Nelson, 1973). And a historical precedent to a dual-stream model of audition goes even farther back to the work of Poljak, who, in 1926, discussed the various subdivisions in "the connections of the acoustic nerve" and came to a conclusion that foreshadowed current dual-stream ideas by the better part of a century:

> The constituent parts of the central auditory system have mostly a double function—viz. to conduct the peripheral auditory sensations to the prosencephalon [forebrain] on the one hand, and on the other, to establish a reflex path for the cochlear stimuli to the motor mechanisms of the brain stem. (Poljak, 1926, p. 468)

The data that drove Rauschecker's claims, as well as those of Deutsch and Roll, concerned the apparent separability of the neural response to the perception of auditory object content versus location, hence the "what" versus "where" distinction. Rauschecker noted that some cells were more responsive to the type of information presented (e.g., different monkey calls), while other cells were more responsive to the location of the sound source (Tian, Reser, Durham, Kustov, & Rauschecker, 2001). Deutsch and Roll came to their conclusion based on the observation that the dichotic fusion of the perception of pitch dissociates from the perception of sound source.

While there is good agreement on the existence of a ventral "what" stream, evidence for a dedicated "where" stream has been mixed (Bregman & Steiger, 1980; Lee & Middlebrooks, 2013; Middlebrooks, 2002; Recanzone, Guard, Phan, & Su, 2000; Smith, Hsieh, Saberi, & Hickok, 2010; Smith, Okada, Saberi, & Hickok, 2004; Smith, Saberi, & Hickok, 2007; Warren & Griffiths, 2003; Zatorre, Bouffard, Ahad, & Belin, 2002). Most of the dissenting voices have questioned the specificity of the spatial hearing system—the idea that there is a dedicated cortical system for spatial hearing. For example, some authors have argued that it is not a spatial computation per se that is carried out in the purported "where" cortical stream, but rather a system that uses spatial information to perform auditory scene segregation, which could easily be viewed as part of a "what" stream (Smith et al., 2010; Zatorre et al., 2002). This debate will not concern us here.

DUAL STREAMS FOR SPEECH

The historical origin of the dual-stream model for speech sits with Wernicke, as noted earlier. Wernicke's model has had its ups and downs since it was proposed in 1874. It enjoyed great initial success with thoughtful elaborations by Lichtheim in 1885 and extensions of the basic functional anatomic ideas into other domains such as apraxia (Liepmann, 1908). But the model fell out of favor as the field shifted away from fairly modular views of mental and neural function (Benton, 1991). Geschwind is credited with reviving the classical model of the anatomy of language in the 1960s (Geschwind, 1965, 1971), but advances in linguistics (Chomsky, 1965, 1986) revealed the model's shortcomings as a complete explanation for the functional anatomy of language. Again, Wernicke's dual-stream model was largely abandoned, leaving the field without a unifying framework.

The modern incarnation of the dual-stream model as proposed by Hickok and Poeppel (2000, 2004, 2007) was inspired not so much by Wernicke (that connection was noticed later), but by the Milner and Goodale dual-stream model in vision, which was quite influential in the late 1990s. Just as Milner and Goodale had updated the "what" versus "where" visual pathways to a "what" versus "how" model, Hickok and Poeppel updated the Rauschecker "what" versus "where" auditory pathway model to a "what" versus "how" framework for speech. Rauschecker and Scott (2009) have proposed their own version of a dual-stream model, including a discussion of both "what" and "how" functions. A recent lesion-based empirical test of the two models favors the Hickok and Poeppel variant (Fridriksson et al., 2016).

Now we turn to a deeper discussion of the dorsal speech stream, including recent developments concerning its anatomy and computational function.

ANATOMY AND PHYSIOLOGY OF THE AUDITORY DORSAL STREAM

The auditory dorsal stream for speech comprises a network of regions, identified primarily on the basis of functional magnetic resonance imaging (fMRI) studies, that includes auditory-related cortices in the superior temporal gyrus/sulcus, motor speech areas in the posterior lateral frontal lobe, and a region in the posterior Sylvian fissure at the parietal-temporal boundary (area Spt) (B. Buchsbaum, Hickok, & Humphries, 2001; Hickok, Buchsbaum, Humphries, & Muftuler, 2003; Hickok, Okada, & Serences, 2009). Spt is hypothesized to serve as the interface between auditory and motor representations of speech (Hickok et al., 2011) in much the same way as regions of the posterior parietal cortex of macaques and humans function as a visuomotor interface (Andersen, 1997; Gallese, Fadiga, Fogassi, Luppino, & Murata, 1997; Grefkes & Fink, 2005; Milner

& Goodale, 1995). Accordingly, Spt has been shown to exhibit auditory-motor response properties, activating both during the perception and (covert) production of speech; indeed, this is a defining property of functional circuit. Spt has also been found to be relatively selective for vocal compared to manual auditory-motor actions. One fMRI study compared Spt activation during listening to simple novel melodies and then either silently humming them back or imagining playing them on a keyboard (participants were skilled pianists): Spt activated more strongly during the humming condition despite identical auditory input (Pa & Hickok, 2008). Spt also appears to be functionally (B. Buchsbaum et al., 2001; B. R. Buchsbaum, Olsen, Koch, & Berman, 2005) and anatomically (Isenberg, Vaden, Saberi, Muftuler, & Hickok, 2012) connected to premotor regions involved in speech production, consistent with what is found for visuomotor integration areas in the parietal lobe (Grefkes & Fink, 2005). It also exhibits distinct activation patterns to auditory and motor phases of the task (Hickok et al., 2009), which argues against a purely auditory or purely motor explanation for its activation pattern.

Damage to this region is associated with conduction aphasia, a syndrome characterized by frequent sound-based errors, which are readily detected by the patient, in otherwise fluent speech production, and difficulty with repeating speech verbatim, particularly nonwords; auditory comprehension is largely preserved (Goodglass, 1992). Functionally, one can conceptualize conduction aphasia as an auditory-motor integration deficit (B. R. Buchsbaum et al., 2011; Hickok et al., 2011). Patients are fluent because frontal lobe motor speech networks are intact; they have good auditory comprehension and can detect their own errors because the speech perception system is intact; what is going wrong is the integration of the two, leading to phonemic errors and difficulty repeating speech. (We take up the details of how this works later in the chapter.) If it is true that conduction aphasia is a deficit of auditory-motor integration and that Spt is a hub in the auditory-motor system, then the lesions in conduction aphasia should involve the Spt region. This is precisely what was found in a recent comparative analysis of Spt functional activation data from more than 100 healthy participants and lesion data from 14 individuals with conduction aphasia (B. R. Buchsbaum et al., 2011). A more recent large-scale lesion analysis of word and nonword repetition more specifically found that repetition impairment is associated with the Spt region (Rogalsky et al., 2015).

As noted, Spt is located within the Sylvian fissure at its posterior-most extent, and in individual subjects typically involves the posterior-medial portions of the planum temporale and/or the parietal operculum, but which can extend laterally toward the crown of the superior temporal and/or supramarginal gyri. Cytoarchitectonically, this location corresponds to area Tpt, a region *not* considered part of unimodal auditory cortex (Galaburda & Sanides, 1980; Smiley et al., 2007; Sweet, Dorph-Petersen, & Lewis, 2005) and therefore consistent with the claim that Spt is not solely auditory but rather auditory-motor.

A recent large-scale lesion study questioned the role of Spt in speech motor planning, suggesting that damage to the region did not predict increases in the number of phonological speech errors in aphasia (Dell, Schwartz, Nozari, Faseyitan, & Branch Coslett, 2013). But this appears to be due to a misspecification of the Spt region of interest in their analysis. An examination of their Figure 4 shows quite clearly that the posterior planum temporale regions is indeed implicated in phonological-level speech errors in aphasia. This study, therefore, provides additional evidence for the role of Spt is speech motor planning at the phonological level.

The anatomical connection between Spt and posterior motor areas is presumed to involve dorsal temporo-parietal-frontal white matter bundles, including the arcuate fasciculus and the superior longitudinal fasciculus (Isenberg et al., 2012; Yagmurlu, Middlebrooks, Tanriover, & Rhoton, 2016). Some models, and one in particular, dubbed "Lichtheim 2," have suggested a role for ventral temporo-frontal pathways, such as the uncinate fasciculus, in speech production (Ueno, Saito, Rogers, & Lambon Ralph, 2011). Although this proposal has been questioned empirically (Roelofs, 2014), it is not inconsistent with the view that the dorsal speech stream and its dorsal white matter connections are a critical part of the auditory-motor speech-production network. Specifically, the dual-stream model has never assumed that the dorsal stream is the only pathway for speech production (note the three separate inputs to the articulatory system in Figure 20.1 and see later in the chapter for computational arguments). It is quite possible, therefore, that ventral stream temporo-frontal pathways play a role speech planning, perhaps serving to activate high-level action plans via lexical-semantic or combinatorial-semantic representations, which are then fine-tuned by lower-level auditory-motor circuits (see following discussion).

COMPUTATIONAL/FUNCTIONAL HYPOTHESES

It has been repeatedly suggested that Spt is an auditory-motor integration area. But what does that mean precisely? And why is auditory-motor integration useful for speech production? Starting with the second question, it is becoming increasingly clear that auditory representations serve as a critical target in speech planning (Guenther, Hampson, & Johnson, 1998; Hickok, 2012, 2014). It is not the only target, as somatosensory representations also play a demonstrable role (Hickok, 2012; Tremblay, Shiller, & Ostry, 2003). A useful way to think about the notion of auditory targets for speech planning is to consider manual grasp planning. When reaching for a cup on a table, the target of that motor gesture is essentially visual—the size, shape, location, and orientation of the cup relative to the limb—and the task of the motor planning system is to configure the limb such that it matches the visual features of the target. If there is no cup, there is no visual representation and thus no target. Speech *appears* to be different in that there is nothing overtly present in the acoustic environment that we direct our speech gestures to "hit." But consider a situation where you place your cup in the same location every day while, say, working on your computer. You don't need to look at the cup to reach for it; in fact, you could do it with your eyes closed. What you do need, however, is a mental representation of that target, which in the case of the cup is the same size, shape, orientation, and in the same location every day. In this case, what we are reaching for as our target is a stored representation of the cup's location, and so on. This is what we are doing in speech—"reaching" for a stored representation of the sound pattern of the words we are trying to articulate. We know that this is the case because if one experimentally manipulates the acoustic targets, for example using altered auditory feedback (Houde & Jordan, 1998), this changes the form of the articulated speech.

The auditory dorsal stream, then, provides the neural means to translate auditory speech targets into accurate motor speech plans. How does it do this? One emerging hypothesis is that it does this via *state feedback control* (Hickok et al., 2011; Houde & Nagarajan, 2011). Feedback-control models generally are those that use sensory feedback to update motor plans. A limitation of models that rely only on overt sensory feedback alone is that such feedback is delayed in time. *State* feedback-control models add a further component, namely, an internal model or prediction of the current dynamic *state* (position and trajectory) of the motor effector, in our case the vocal tract. Overt sensory feedback is used to train the internal model such that it can make predictions (often called "forward" predictions) about the current state of the motor effector given its previous state and current motor commands. This allows the system to make predictions regarding the sensory consequences of motor plans, which facilitates error detection and correction. It has been argued further that state feedback control in speech planning allows for error detection and correction even prior to articulation (Hickok, 2012). The basic idea is that during speech planning, a target word form is activated in sensory cortex and a motor plan is activated in motor cortex; the sensory consequences of the motor plan can then be checked against the target via forward prediction and corrected, if need be, prior to articulation. The basic computational architecture has been extended in a further model called *hierarchical state feedback control* that goes beyond auditory-motor interaction by including a lower hierarchical planning level involving somatosensory targets in somatosensory cortex, motor coding in primary or pre-motor cortex, and an interface involving the cerebellum (Hickok, 2012).

Coming back to the role of Spt in this computational framework—our first question at the beginning of this section—it has been argued that Spt is part of the internal model, specifically, the component that computes a transform between auditory and motor speech representations (Hickok, 2012; Hickok et al., 2011). Figure 20.2 presents a graphical depiction of the proposed architecture (Hickok et al., 2011). The model assumes that in the mature system (i.e., one in which the internal model has been robustly learned) auditory target and motor plans can be activated in parallel via inputs from the lexical system, which may be achieved anatomically via distinct white matter pathways. Motor plans are then checked against their auditory targets via forward prediction, and correction signals are generated as needed. Anatomically, it is assumed that the auditory phonological system localizes to the superior temporal sulcus, that the motor phonological system localizes to premotor cortex, and the auditory-motor translation system localizes to area Spt.

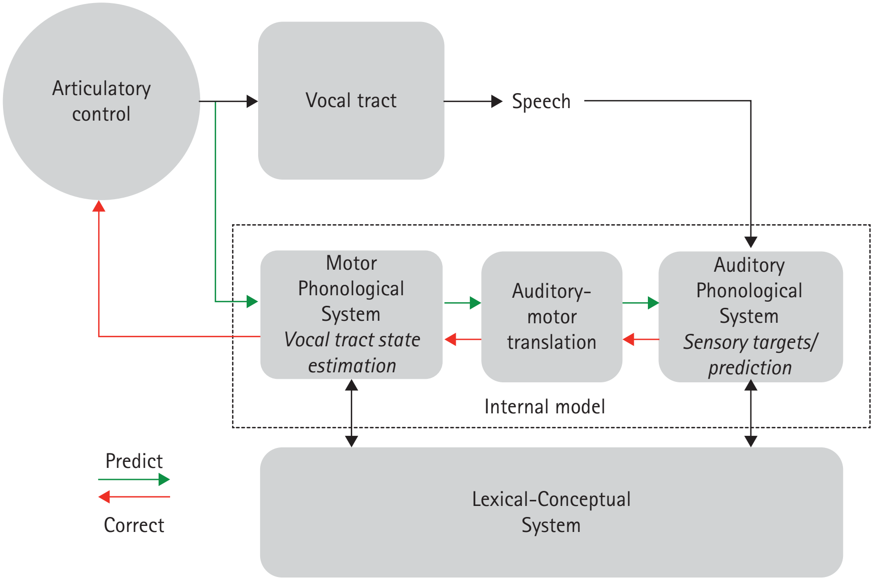
Articulatory control
Vocal tract
Speech
Motor Phonological System *Vocal tract state estimation*
Auditory-motor translation
Auditory Phonological System *Sensory targets/ prediction*
Internal model
Predict
Correct
Lexical-Conceptual System

FIGURE 20.2. A state feedback-control model for speech processing.

Source: Reprinted with permission from Hickok et al. (2011).

A COMPUTATIONAL TEST OF ONE COMPONENT OF THE STATE FEEDBACK-CONTROL ARCHITECTURE

From a psycholinguistic standpoint, the idea that the phonological system is split into two components is not typical of most models of speech production, including the dominant computational approaches (Dell, 1986; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Levelt, 1999; Levelt, Roelofs, & Meyer, 1999). There is some precedent, however, in the neuropsychological literature where patterns of dissociation have led to the claim that there exist distinct phonological input and output lexicons (Jacquemot, Dupoux, & Bachoud-Levi, 2007). Still, one would like to see additional psycholinguistic/computational evidence for the proposed architecture. One approach is to modify existing successful computational models of speech production so that they approximate the architecture of the state feedback-control model (i.e., contain separate auditory- and motor-phonological components), and then assess whether the modified model better explains the data.

The recently developed SLAM (semantic lexical auditory motor) computational model does just this (Walker & Hickok, 2016a Figure 20.3). SLAM is a modification of the semantic-phonological (S-P) model, which has proven quite successful in accounting for distributions of naming errors in aphasia (Dell, Martin, & Schwartz, 2007; Dell et al.,

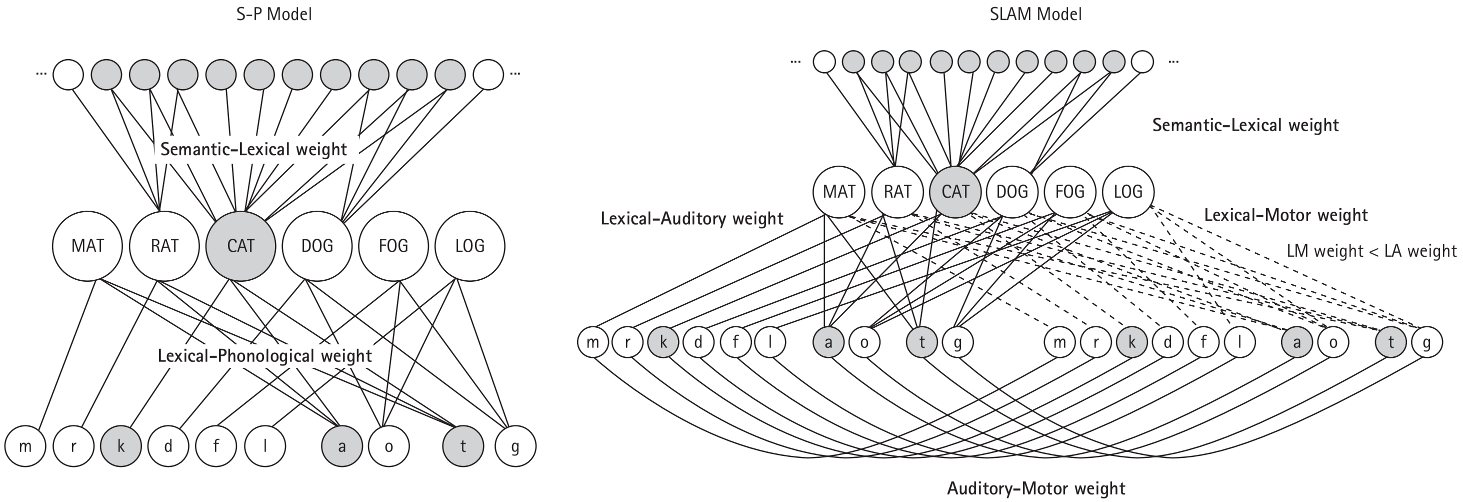
S-P Model
...
...
Semantic-Lexical weight
MAT
RAT
CAT
DOG
FOG
LOG
Lexical-Phonological weight
m
r
k
d
f
l
a
o
t
g
SLAM Model
...
...
Semantic-Lexical weight
MAT
RAT
CAT
DOG
FOG
LOG
Lexical-Auditory weight
Lexical-Motor weight
LM weight < LA weight
m
r
k
d
f
l
a
o
t
g
m
r
k
d
f
l
a
o
t
g
Auditory-Motor weight

FIGURE 20.3. Graphic depiction of the semantic-phonological (S-P) and semantic lexical auditory motor (SLAM) models.

1997; Nozari, Kittredge, Dell, & Schwartz, 2010). The S-P model is a two-step model of word production where the first step involves lexical or lexeme selection and the second step involves phonological selection. The model has been implemented in a connectionist network comprising three layers: an input semantic feature layer, a middle lexical selection layer, and an output phonological layer. By adjusting only two connection strength parameters, the semantic-lexical weight and the lexical-phonological weight, the model can approximate the pattern of errors in individual aphasic patients with reasonably high accuracy.

SLAM made one modification to the S-P model: it split (actually duplicated) the phonological layer into an auditory- and motor-phonological layer, with the latter serving as the output layer. The question that was asked is whether SLAM provided a better fit to the aphasia naming data than S-P. The answer was yes. Overall, SLAM did a better job of fitting the data than S-P and substantially outperformed S-P for patients with conduction aphasia, which fits nicely with the preceding discussion regarding the importance of auditory-motor interaction is speech production and its link to conduction aphasia (Walker & Hickok, 2016a). This finding provides an additional source of support for the architectural assumptions of the state feedback-control framework.

As with any new theory, SLAM has its detractors. Goldrick (2016) argues that SLAM's improvement over SP is merely a result of approximating a different model of production in which the phonological layer is broken down, not into auditory and motor components, but into lexical (higher-level) and post-lexical (lower-level) layers (Goldrick & Rapp, 2007). This is an important point that highlights the fact that SLAM is not a complete model of speech production in that it does not model all of the hierarchical complexity of the system. For example, SLAM does not even attempt to model all the layers proposed in the hierarchical version of the state feedback-control model (Hickok, 2012). That said, a computational evaluation of Goldrick's claims showed that simply adding an additional post-lexical layer to the SP model does not yield the same fit improvement over SP that was found with SLAM (Walker & Hickok, 2016b); it is the additional layer arranged in a particular *architecture* that provides the boost.

Conclusions

Dual-stream frameworks for sensory processing have proven to be highly successful and long-lived in vision and audition, suggesting that this broad architecture is a general principle of sensory neurocomputational design. The success of such frameworks has been shown in speech and language, perhaps as a prototypical case. Much progress has been made over the last decade and half in mapping the neuroanatomy and computational function of the dorsal, sensorimotor speech stream. The field has progressed from the simple auditory-motor connection proposed by Wernicke in the 1870s to the specification of several nodes in a cortical network including temporal, temporoparietal junction (Spt), and posterior frontal regions and with new hypothesized computational roles and anatomical pathway connectivities. These networks are beginning to make serious contact with psycholinguistics models and with analogous networks outside of speech and language. Given the trajectory of recent progress, there is every reason to believe we will see significant further advances in the coming years.

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PART IV

CONCEPTS AND COMPREHENSION

CHAPTER 21

NEURAL REPRESENTATIONS OF CONCEPT KNOWLEDGE

ANDREW J. BAUER AND MARCEL A. JUST

Introduction

A key goal of cognitive neuroscience is to delineate the nature, content, and neuroanatomical distribution of the neural representation of concept knowledge, which underlies human thought, communication, and daily activities, from small talk about well-worn topics to the learning of quantum physics. Accordingly, research that identifies the neural systems that underlie different categories of concept knowledge (e.g., concepts of animals, tools, and numbers) has made significant advances, particularly research on object concepts (see Martin, 2007). Earlier methods that investigated the neural representation of concept knowledge included the study of deficits in concept knowledge in brain-damaged patients, as well as univariate analyses of activation in the healthy brain using functional magnetic resonance imaging (fMRI).

More recent neuroimaging research is uncovering the fine-grained spatial patterns of brain activation (e.g., multi-voxel patterns) evoked by individual concepts. These brain-reading or neurosemantic studies have generally shown that the spatial pattern of activation that is the neural signature of the concept is distributed across multiple brain regions, where the regions are presumed to encode or otherwise process different aspects of a concept. Conventional linear model-based univariate analyses of activation levels (e.g., statistical parametric mapping in fMRI; Friston et al., 1994), which do not take account of multi-voxel patterns, have typically detected only a small number of brain areas involved in concept representation. Although the idea of multivariate pattern analysis of activation data is not new (Cox & Savoy, 2003), neurosemantic methods have enabled a paradigm shift in studying how concepts are neurally represented.

This chapter summarizes some key research findings that have characterized where and how different types of concept knowledge are represented in the brain. The focus of this chapter is on studies of the neural representations of concepts, rather than on the brain regions that support and mediate semantic processing (see Binder, Desai, Graves, & Conant, 2009, for a meta-analytic review of the neural systems that underlie semantic processing; for other approaches, see, in this volume, Musz & Thompson-Schill, Chapter 22, and Garcea & Mahon, Chapter 23). Because most of the neuroimaging research reviewed here used blood oxygenation level-dependent (BOLD) fMRI (see Heim & Specht, Chapter 4 in this volume), *brain activation* henceforth refers to data collected using fMRI unless stated otherwise (e.g., magnetoencephalography, or MEG; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume).

The majority of this chapter details how neurosemantic research has illuminated various prominent questions in ways that build on the results of conventional data analytic methods. Some of these questions are the following: Do neural concept representations evoked by pictures differ from those evoked by words? What types of information are encoded in a given neural concept representation? To what extent are neural representations common across different people? What are the differences between the neural representations of abstract versus concrete concepts? The chapter includes a brief survey of the neurosemantic methods that are used to anatomically localize and characterize the kinds of information that are neurally represented.

The chapter ends by summarizing the results of neurosemantic studies that characterize the changes in neural concept representations during the learning of new concepts, a topic that has received little attention. The findings from these studies provide a foundation for cognitive neuroscience to trace how a new concept makes its way from the words and pictures used to teach it, to a neural representation of that concept in a learner's brain. Monitoring the growth of a new neural concept representation has the potential for further illuminating how concepts are stored and processed in the brain.

THE SPATIALLY DISTRIBUTED NATURE OF A NEURAL CONCEPT REPRESENTATION

Human beings are capable of thinking about a vast number of concepts at various levels of abstraction. This variety of ideas and abstractions is reflected in everyday vocabulary and technical terminology (although not all concepts are necessarily expressible in language). One approach to characterizing concepts in terms of semantically related words is to construct a lexical database, as the authors of WordNet have done. WordNet is an English lexical database in which nouns, verbs, adjectives, and adverbs are grouped into sets of synonyms, where each set constitutes a distinct individual concept. It is a semantic network that consists of 117,659 concepts, each of which is connected to other concepts through a chain of semantic relations (WordNet 3.1, http://wordnet.princeton.edu). WordNet was originally created to be consistent with hierarchical propositional theories of semantic memory, which postulate that concepts are organized hierarchically from general to specific concepts (e.g., Collins & Quillian, 1972). The most common type of semantic connection between words is the hierarchical "is-a" relation. The concept *chair*, for example, is related to *furniture* by an "is-a" connection. As indicated in WordNet, concepts that human beings can think about range from thoughts of physical objects, such as organisms and geological formations, to abstractions, such as psychological states and mathematical entities.

The ability to study how this range of concepts is represented neurally has only recently become possible since the development of data analytic methods that can detect a correspondence between a distributed brain activation pattern and an individual concept. Neurosemantic research initially focused on only a small fraction of this range of concepts, namely animate and inanimate object concepts such as animals, faces, and tools and other manmade objects (e.g., Haxby et al., 2001; Mitchell et al., 2003; for an account of early neurosemantic research, see Haxby, 2012). These choices of concept categories were motivated by previous clinical studies of object category-specific agnosia, and also by univariate analysis-based neuroimaging findings that elaborated on the clinical results. Clinical studies found that relatively selective cortical damage was associated with a disproportionate deficit in concept knowledge for one of a small set of categories (e.g., animals or tools; for a review of the clinical literature, see Capitani, Laiacona, Mahon, & Caramazza, 2003). This body of work suggested that concept categories were subserved by only a few brain regions. However, mapping large brain areas to single-concept categories does not provide an account of neural concept representations that scales to the huge number of concepts that must be represented. A more efficient scheme that can accommodate vast numbers of concepts would be a pattern-encoding scheme, such that the neural representation of a concept corresponds to a spatial pattern of activation of many individual voxels, each displaying a level of activation that is characteristic of the concept. Early neurosemantic research provided the empirical basis for pattern encoding by indicating that concept knowledge might be represented in neural populations distributed over a large number of brain areas.

Since the early fMRI research on concrete object concepts, neurosemantic research has replicated the finding that neural concept representations span multiple brain regions, and has revealed the activation patterns associated with other types of concept knowledge, such as emotions (Baucom, Wedell, Wang, Blitzer, & Shinkareva, 2012; Kassam, Markey, Cherkassky, Loewenstein, & Just, 2013), numbers (Damarla & Just, 2013; Eger et al., 2009), personality traits (Hassabis et al., 2013), and social interactions (Just Cherkassky, Buchweitz, Keller, & Mitchell, 2014). In one study, close to 2,000 individual object and action concepts were each localized to multiple brain areas (Huth, Nishimoto, Vu, & Gallant, 2012). Figure 21.1 shows that the neural representations of these object and action concepts each reside in multiple areas distributed throughout the brain. The figure contains color-coded mappings between various concepts and their representations in various areas. For example, concepts related to communication (cyan) were found to be represented in auditory sensory cortex in the temporal lobe and a frontal area that includes Broca's area, a canonical language region.

The main theoretical interpretation regarding spatially distributed neural representations is that the multiple brain areas that conjointly represent a given concept

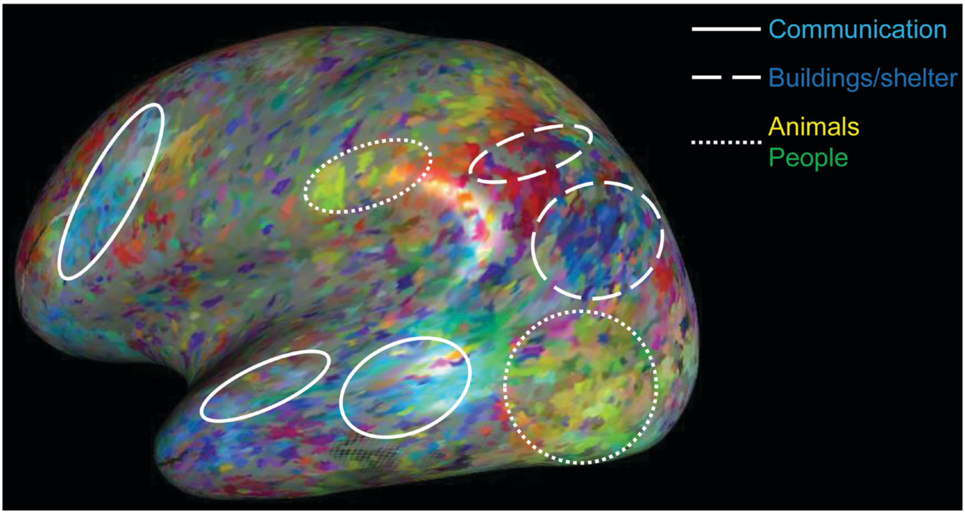

FIGURE 21.1. Neural concept representations are distributed throughout the brain. In Huth et al. (2012), 1,705 individual object and action concepts that appeared in movies were each found to be represented over multiple brain areas. Indicated by the three types of ellipses are the major brain areas associated with some of the superordinate categories of these object and action concepts. Auditory sensory cortex in the temporal lobe and a frontal language area were associated with communication; postcentral gyrus (sensation and movement) and occipitotemporal cortex (visual) were associated with biological entities; and parietal (spatial) and occipital areas were associated with buildings and shelter.

Source: The figure corresponds to one participant's inflated brain, and was extracted from http://gallantlab.org/semanticmovies.

correspond to the brain systems that are involved in the physical and mental interaction with the concepts' referents. For example, the concept of a knife entails what it looks like, what it is used for, how one holds and wields it, and so on, resulting in a neural representation distributed over sensory, perceptual, motor, and association areas.

These findings from multivariate analyses build on and are consistent with past univariate analysis-based research. For example, nouns that refer to physically manipulable objects such as a knife have been shown to activate left premotor cortex in right-handers (Lewis, 2006). In addition to left premotor cortex, activation has been observed in additional regions but at lower magnitudes, a result that hinted at the greater spatial distribution of concept knowledge in the brain (Chao, Weisberg, & Martin, 2002).

In behavioral cognitive science, a concept is often treated as a mental representation that specifies some of the dimensions of a real-world phenomenon (e.g., visual or tactile properties of an object), in addition to the relations among those dimensions (see Barsalou, 1992, for a discussion of the nature of concept representation). Consistent with this approach is the finding that multiple brain regions, which encode different dimensions, collectively contain the information about a single concept. For example, the concept *cat* might include dimensions of cats that are common across different breeds, such as general body shape, locomotion, diet, temperament, and so on. These properties should be detectable in the brain activation pattern associated with the concept *cat*. Several studies have used regression models to predict the activation pattern of a given object concept, based on how different voxels are tuned to various dimensions of objects and on how important those dimensions are to defining a given object concept. Accurate predictions have been made using properties of objects generated by human participants (Chang, Mitchell, & Just, 2011) or extracted from text corpora such as web-based articles (Mitchell et al., 2008; Pereira, Botvinick, & Detre, 2013). In addition, an MEG study that used properties generated by participants predicted the spatial pattern of evoked magnetic fields associated with an object concept (Sudre et al., 2012).

The discussion here has assumed that sensorimotor systems in the brain store or otherwise process information that is integral to the comprehension of a concept, particularly object concepts. In this view, the representations of some concepts entail body-object interaction information; that is, they are *embodied* representations (Barsalou, Santos, Simmons, & Wilson, 2008). Some alternative theories hold that the brain activation observed in sensorimotor regions reflects imagery or simulated motion that occurs only after conceptual processing, and that fundamental concept meaning is encoded only in association areas such as the anterior medial temporal lobe (for a review of the competing theories, see Mahon & Caramazza, 2008; Meteyard, Cuadrado, Bahrami, & Vigliocco, 2010; and Kiefer & Pulvermüller, 2012). However, several studies using words referring to concrete objects have shown that sensorimotor activity evoked by the words occurs too early to originate from imagery explicitly generated by the participants (e.g., Kiefer, Sim, Herrnberger, Grothe, & Hoenig, 2008; see also Martin, 2007), providing some evidence for the embodied view of the representations of certain concepts.

Characterizing the Semantic Dimensions That Underlie Neural Concept Representations

A central objective of neurosemantic research is to determine some of the main semantic dimensions that underlie the neural representation of a given concept. This objective can be reached by reducing an activation pattern's dimensionality (often consisting of the activation levels of tens to hundreds of voxels) to determine the main factors underlying the representation. For example, in a study of emotions (e.g., anger, disgust, envy, fear, happiness, lust, pride, sadness, and shame), factor analysis of the activation data indicated that each emotion was represented with respect to four underlying dimensions: *valence, arousal, sociality*, and *lust* (Kassam et al., 2013). Each of these dimensions was further localized to plausible networks of brain regions. *Arousal*, for example, was localized to basal ganglia and precentral gyrus, which have previously been implicated in action preparation. The *sociality* dimension (which was not previously recognized as a core dimension of emotions) was traced to anterior and posterior cingulate cortex, two default mode network regions previously shown to be involved in social cognition. Although most of the dimensions were traced to brain areas previously implicated by univariate analysis-based research, it is notable that this single neurosemantic study uncovered results comparable to the results of multiple conventional neuroimaging studies.

A similar analysis of the activation patterns evoked by 60 object concepts identified three key dimensions: *manipulation* (e.g., tools and other manipulable objects), *eating* (e.g., vegetables, kitchen utensils), and *shelter* (e.g., dwellings, vehicles) (Just, Cherkassky, Aryal, & Mitchell 2010). *Manipulation* was associated with left postcentral/supramarginal gyrus and left inferior temporal gyrus, which have previously been implicated in the processing of tool concepts (Lewis, 2006). The *eating* dimension was traced to left inferior temporal gyrus and left inferior frontal gyrus, which revealed a link between representations of tool concepts (namely kitchen utensils) and representations of face- and jaw-related actions (Hauk, Johnsrude, & Pulvermüller, 2004). Finally, the *shelter* dimension was traced to bilateral parahippocampal gyrus and bilateral precuneus. The parahippocampal gyrus is well known to activate in response to information about dwellings and scenes (e.g., Epstein & Kanwisher, 1998), and the precuneus areas were anatomically close to retrosplenial cortex, which is thought to be involved in the comprehension of a scene within a larger environment (for a review on retrosplenial cortex, see Vann, Aggleton, & Maguire, 2009).

One study greatly expanded the range of concepts whose neural representations were uncovered by collecting activation data as participants watched several hours of movies (Huth et al., 2012). The investigators used WordNet to label 1,364 common objects (nouns) and actions (verbs) that appeared in the movies, and an additional 341 superordinate categories were inferred using the hierarchical relationships in WordNet (e.g., *canine* and *mammal* were added if *wolf* was an object that appeared in a movie). Data reduction yielded four dimensions that were interpretable: *mobility/animacy, sociality* (e.g., words about people and communication), *civilization* (e.g., people, man-made objects, vehicles), and *biological entities*. Interestingly, these dimensions partially overlap with the dimensions revealed by the two other neurosemantic studies that separately investigated object and emotion concepts (described earlier). Thus, different studies using different methodologies appear to be converging on a common set of underlying neural dimensions of representation.

Integration among a Concept's Semantic Dimensions

A central aspect of a concept is how the different semantic dimensions relate to each other. Although some of the underlying dimensions of certain types of concept knowledge are being identified, much less is known about the relations among the dimensions. For example, some of the key dimensions of concrete objects appear to be *manipulation, eating*, and *shelter*. Is a neural representation of an object concept then anything more than the sum of the representations of the concept's individual dimensions? For example, would there be some indication in a neural representation that a gingerbread house is fundamentally different from a cafeteria building, even though both involve information related to *eating* and *shelter*? It is unclear whether relations among the dimensions of a concept are represented in brain areas that are spatially distinct from the locations of the individual dimensions (e.g., convergence zones; Damasio, 1989), or whether relational information is somehow encoded in a distributed way across the set of areas that also represent the individual dimensions.

A multivariate analysis of the activation in a visual perception task investigated which brain areas encode the conjunction of separate dimensions (Seymour, Clifford, Logothetis, & Bartels, 2009). The dimensions that were combined were the color and direction of motion of a set of dots, which were either green or red and rotated either clockwise or counterclockwise. The specific conjunction of color and direction of motion of a given item was found to be represented in multiple areas of early visual cortex that also encode the individual dimensions, indicating that these areas contain both a representation of the individual dimensions and the relation between the dimensions. This integration of information might be a critical aspect of the representation of a cohesive percept.

On the other hand, there is also evidence that the relations among a concept's component dimensions are represented exclusively within specific high-order brain areas or convergence zones. An anterior temporal lobe region has been suggested as a site of dimension integration because it is innervated by different sensory modalities, and because abnormal functioning of this region is associated with impairments to semantic processing, but not to the performance of non-semantic cognitive tasks (Pobric, Jefferies, & Ralph, 2007; Patterson, Nestor, & Rogers, 2007). Coutanche and Thompson-Schill (2014) demonstrated that the conjunction of an object's dimensions was encoded in a multi-voxel pattern in anterior temporal lobe, but not in the areas that separately represent the individual dimensions. Specifically, the depicted objects were fruits and vegetables, and the dimensions were color and shape (whose representations were investigated in fusiform gyrus and occipitotemporal cortex, respectively). Furthermore, the representation of the conjunction was detectable by the investigators only when each dimension's representation could be detected, strengthening the evidence for the conclusion that the anterior temporal region represents the integration of individual components.

Thus the evidence is mixed as to whether the integration of information about separate dimensions is represented in high-order brain regions versus in the network of areas that underlie the individual dimensions. It is also possible that integrated information is encoded in both representational formats.

NEUROSEMANTIC METHODOLOGY

Neurosemantic data analyses attempt to detect multi-voxel patterns of brain activation that correspond to the thoughts of concepts. One virtue of this approach is that it adheres to the fundamental principle that thinking is a network function involving multiple brain systems, including thinking about a concept. A second advantage of this approach is that it bestows a greater sensitivity for discovering the underlying phenomenon, by virtue of concurrently assessing the activations of many voxels with similar activation patterns for the stimuli at hand, regardless of the voxels' proximity to each other. One phenomenon whose discovery has benefited from this greater sensitivity is the representation of different concepts that are in the same superordinate semantic category. The greater sensitivity of multi-voxel analysis enables researchers to distinguish between the activation patterns of such concepts (e.g., distinguishing between different animal concepts such as a primate and bird; Connolly et al., 2012); that is, the newer methods can compare patterns of activation between individual concepts in spatially distributed voxels. With the use of neurosemantic methods, a finding of various related concepts eliciting unique yet similar activation patterns over a set of brain areas constitutes suggestive evidence that those brain areas store or otherwise process the meanings of the concepts.

By contrast, conventional univariate analyses often report the magnitudes of activation of individual voxels that are averaged over a region of interest, requiring spatial proximity among the voxels that are grouped together (see Poldrack, 2007). Univariate analysis is sometimes not sensitive enough to distinguish between similar experimental conditions because the mean activation level of a set of voxels is often equivalent between similar conditions. Univariate analysis is useful for identifying the brain areas that are *involved* in the processing of some class of concepts, by determining whether an area's activation level is elevated. Figure 21.2 depicts a hypothetical scenario in which the greater sensitivity of multivariate analysis enables distinguishing between two similar conditions, whereas univariate analysis finds no difference between the conditions but establishes for each condition an elevation in mean activation level (for a detailed comparison of the methods, see O'Toole et al., 2007, and Mur, Bandettini, & Kriegeskorte, 2009). Of course, "sensitivity" is assessed with respect to the phenomenon of interest, and there are doubtless phenomena other than multi-voxel activation patterns corresponding to concepts for which univariate analyses may be more sensitive (Coutanche, 2013; Davis et al., 2014).

One commonly used technique in neurosemantic studies is discriminative multivariate pattern classification analysis (MVPA). A classifier is an algorithm that is trained to associate an activation pattern with each of the stimuli (or classes of stimuli) and is subsequently reiteratively tested (using a procedure called cross-validation) on an independent data set (for a tutorial, see Pereira, Mitchell, & Botvinick, 2009, and Norman, Polyn, Detre, & Haxby, 2006). Logistic regression is an example of a discriminative classifier. The main strength of MVPA is its concurrent consideration of the activations of multiple voxels, regardless of their relative locations in the brain. MVPA has been used to discover neural representations of various types of information, such as covert intentions in prefrontal cortex (Haynes et al., 2007), visual imagery of simple shapes in occipitotemporal cortex (Stokes, Thompson, Cusack, & Duncan, 2009), and episodic memories in the hippocampus (Chadwick et al., 2010). The accuracy of the classification is a measure of the discriminability of the stimuli (or classes of stimuli), sometimes

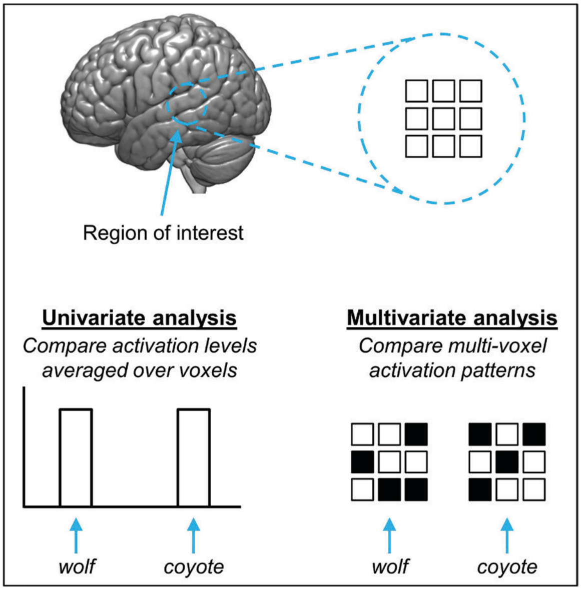
Region of interest
Univariate analysis
Compare activation levels averaged over voxels
Multivariate analysis
Compare multi-voxel activation patterns
wolf
coyote
wolf
coyote

FIGURE 21.2. Comparison of univariate and multivariate data analysis. A hypothetical scenario in which multivariate analysis (*right*) reveals that the multi-voxel *pattern* of activation levels in left primary auditory cortex differs between two animal concepts (i.e., two animals that make similar sounds). Univariate analysis (*left*) shows that the level of activation *averaged* over the set of voxels is the same between the two concepts, but establishes an elevation in mean activation for both concepts.

computed as the rank accuracy, or the normalized percentile rank of a correct stimulus in the classifier's ranked output (Mitchell et al., 2004). Here, chance level is a normalized rank accuracy of 0.5, where the correct classification response occupies the middle rank among all possible responses. The obtained accuracy can then be compared to a distribution of accuracies that would be obtained by chance (typically obtained by Monte Carlo simulations).

Methods That Assess the Semantic Content of Neural Representations

Importantly, what is neurally represented is not just the meaning of a concept, but also the perceptual form of the word or picture that refers to the concept. The perceptual form is represented in primary and secondary sensory brain regions. Thus, simply obtaining accurate classification of an activation pattern does not ensure that the pattern encodes concept meaning. To substantiate that a given activation pattern corresponds to the meaning of a concept, it is sometimes useful to show that the set of correlations among the activation patterns bears a clear relation to behavioral judgments of similarity among the concepts. A statistically reliable correlation between the two sets of inter-item similarities would provide converging evidence that concept meaning underlies the systematic differences in the activation data. Another way to ensure that an MVPA is identifying the representation of a concept—and not the representation of the picture or word that evokes it—is to exclude sensory and early perceptual area voxels from the analysis.

Although discriminative classifiers are extremely useful for associating brain areas with stimuli, they do not easily lend themselves to predictive or generative modeling, as a generative classifier can do. A generative classifier is useful if there is a need to predict the activation that will be evoked by a new stimulus. The central property of a generative classifier is its postulation of a set of intermediate variables between the stimulus and activation that modulate the activation as a function of the properties of the stimulus. The classic method for predictive modeling is regression, which can be used to predict the activation of a yet unseen stimulus, based on how its properties modulated the activation of the stimuli on which the model was trained. Predictive regression models can provide converging evidence for the neural representation of concept meaning in terms of the postulated semantic dimensions that underpin the neural representation of a concept. A model is first estimated of how a set of voxels is tuned to different dimensions (e.g., the size or animacy of an object). A prediction is then made of a concept's activation pattern based on the weighted importance of the dimensions in the representation of that concept. The generalizability of the model can be assessed by testing the predicted activation pattern of any concept that is definable by the dimensions included in the model (Naselaris, Kay, Nishimoto, & Gallant, 2011). As mentioned previously, it is possible to accurately predict an object concept's activation pattern using properties of objects generated by human participants (Chang et al., 2011; Sudre et al., 2012). This approach has also been used to investigate how different voxels in visual brain areas are tuned to different visual features (Kay, Naselaris, Prenger, & Gallant, 2008). The general goal of this approach is to relate concept properties to one or more areas of activation.

Another methodology that can help characterize the neural representation of a concept is representational similarity analysis (RSA), which assesses the neural similarity between all pairs of items and relates the resulting similarity structure to the activation patterns (see Musz & Thompson-Schill, Chapter 22 in this volume). Some researchers use the idea of an *n*-dimensional representational space, in which the distance between a given pair of concepts approximates the degree of similarity between the concepts' activation patterns. If the multi-voxel activation pattern for two concepts is known, then the similarity (or distance) between them can be computed and the full set of inter-item distances can be used to specify the space. In this approach, the set of inter-concept distances can reveal the kinds of information that underlie the representations (see Kriegeskorte, Mur, & Bandettini, 2008, for a tutorial on RSA). For example, Figure 21.3 shows the similarity structure of six biological species concepts, corresponding to two different brain areas. The similarity structure of the concepts differs between the two areas, indicating that the information that is encoded or otherwise processed differs between the areas. The information represented in occipitotemporal cortex is organized

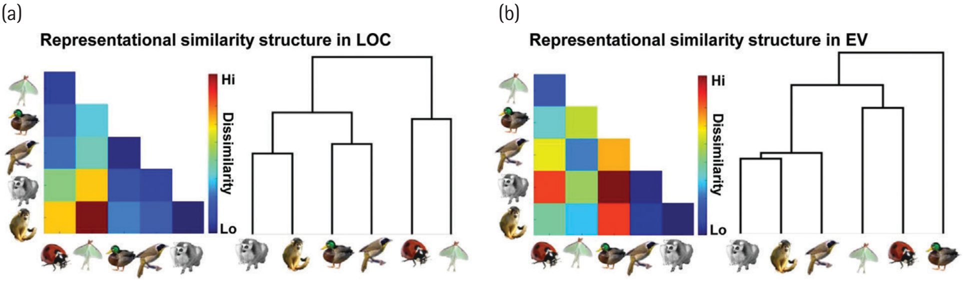

FIGURE 21.3. Representational similarity structures in different brain areas reveal differences in the types of information neurally represented therein. Shown for two different brain areas are the dissimilarities between all pairs of biological concepts' activation patterns, and the hierarchical structure that emerges from these dissimilarities. The representational dissimilarity between any two concepts was computed as 1 – the correlation between their activation patterns. (A) Lateral occipital complex (LOC), a high-order visual brain area that here represents information corresponding to species category. (B) Early visual cortex (EV), a collection of brain areas that process low-level visual features, which seems to encode visual properties of the concepts that do not correlate with species category.

Source: The figure was adapted with permission from Connolly et al. (2012).

with respect to species category, given that the neural dissimilarity is lowest between the two primates, between the two birds, and between the two insects. On the other hand, the information in early visual cortex seems to encode visual properties of the concepts that do not correlate with species category. In this way, representational similarity structures have the potential to reveal the underlying dimensions along which concepts are organized in the brain.

The capacity of RSA to reveal the semantic content encoded in neural representations depends in part on the measures of dissimilarity between a pair of vectors of activation levels, such as correlational measures (e.g., 1—the Pearson correlation between multi-voxel activation patterns), or geometric distances (e.g., Euclidean or Mahalanobis distance). Another type of measure of neural dissimilarity is the classification accuracy in a classifier's confusion matrix. A comparison of these dissimilarity measures for RSA has revealed that continuous distances (i.e., correlation and geometric distances) produce more reliable results than classification accuracies, largely because classification accuracies are obtained from binary decisions that discard continuous dissimilarity information (Walther et al., 2016). Furthermore, dissimilarity measures that are cross-validated across subsets of activation data provide an interpretable zero point against noise.

Apart from RSA, other data-driven, exploratory methods are used to characterize the informational content contained in neural representations. To identify key underlying dimensions from a large set of voxels spanning multiple brain regions, dimension reduction techniques, such as principal or independent components analysis or factor analysis, are useful (see Heim & Specht, Chapter 4 in this volume). These dimension reduction methods can separate the activation patterns into smaller sets of voxels (which maximize the amount of total or shared variance explained in the data), where each set is associated with one or more of the dimensions (e.g., Just et al., 2010; Kassam et al., 2013). If some of the voxels associated with one of the dimensions are localized primarily in the motor cortex, for example, then it is likely that motor action constitutes part of the semantic content of that dimension.

Even with the use of advanced neurosemantic methods, caution may be needed in concluding that the activation pattern in a set of brain regions represents the meaning of a particular concept because of the notorious difficulty in distinguishing representation from process (Anderson, 1978). It is sometimes difficult to distinguish whether an activation pattern corresponds to where and how information is *stored*, versus corresponding to the processes that operate on the representation. Measurement of a neural concept representation requires evoking an activation pattern, thus potentially conflating representation and process; for example, the content of a neural concept representation might be a facet of processing related to selective attention. Selective attention has been shown to change the tuning characteristics of occipitotemporal and frontoparietal cortex for the objects shown in a movie (Çukur, Nishimoto, Huth, & Gallant, 2013). A way to address this type of difficulty might be to test whether characteristics of the activation patterns vary as a function of the nature of the task that the participants perform. It will be useful for future research to characterize neural concept representations in a way that takes into account the nature of the processing that evokes that concept, for example in sentence comprehension (Poeppel, 2012), story comprehension (Wehbe et al., 2014), and problem-solving (Anderson & Fincham, 2014).

Methods of Evoking a Neural Concept Representation

Various methods have been used to evoke the brain activation that underlies a concept. They vary with respect to three characteristics: (1) the amount of time allotted for a participant to process and think about a concept; (2) the nature of the task that the participant is asked to perform; and (3) the modality of the stimulus used to evoke a concept.

Each method of evoking a concept has its own profile of advantages and disadvantages; for example, allotting more time to think about a concept can yield more robust signal in the activation data and thus greater classification accuracy. However, if there is no instruction to think about a concept in a certain way, greater thinking time may result in variation in the activation across the repetitions of a concept, due to the different ways in which a participant may think about a concept. Furthermore, an instruction to think about a concept in a particular way or context may induce an unrepresentative instantiation of the concept (e.g., thinking about *dog* as a participant in a race).

A study in which the participants were presented the same emotion concepts under different task instructions provided evidence of the commonality of the neural representation across two very different task conditions (Kassam et al., 2013). In one condition, participants were presented with emotion words (such as “anger”) and were instructed to evoke thoughts and feelings associated with each emotion. In a different condition, participants passively viewed pictures that evoked disgust. A classifier that was trained on the activation evoked by the emotion words (which included "disgust") was then able to identify the disgust evoked by the pictures with good accuracy. This finding provided evidence that, at least in this case, the brain activation patterns corresponding to disgust in these two very different conditions were fairly similar to each other. It would be useful to see many other concept representations compared, under many different conditions, to determine which facets of a neural representation are always activated and which are modulated by the nature of the evoking task.

Influences of Language on Neural Concept Representations

One task effect of long-standing interest involves the difference in the content of a neural concept representation depending on whether the evoking stimulus is a word versus a picture. For example, is a picture of a screwdriver more likely than the word "screwdriver" to evoke a specific, potentially unrepresentative instantiation of the concept *screwdriver*, especially if the picture is richly detailed? A resolution of this issue would provide a theoretical framework to account for the results of numerous studies that use words, pictures, movies, or other stimuli to evoke a concept.

A neurosemantic study uncovered suggestive evidence that the central aspects of a neural concept representation are to a large extent independent of the stimulus used to evoke the concept (Shinkareva, Malave, Mason, Mitchell, & Just, 2011). In this study, it was possible to classify the activation pattern of an object concept cued by the noun naming the object with a classifier trained on the activation pattern of the same concept evoked by a simple line drawing, and vice versa. Specifically, the classifier determined whether a given object concept referred to a tool or dwelling. Although this study assessed only a small number of items from only two categories, it is suggestive of a common core neural representation that is evoked regardless of the stimulus modality.

In Shinkareva et al. (2011), it was possible to classify the words or pictures using activation from the language system (left inferior frontal gyrus) and also from sensorimotor brain regions. These results are consistent with the Language and Situated Simulation theory of semantic processing (akin to the embodied cognition approach), which holds that a concept activates both the language system and the same sensorimotor regions that are active during actual interaction with the concepts' referents (Barsalou et al., 2008; Simmons, Hamann, Harenski, Hu, & Barsalou, 2008).

Despite there being a shared core of the neural representation between pictures and words referring to a concept, there is evidence of differences in the neural concept representations. A possible asymmetry between pictures and words is that pictures evoke not only a concept's core meaning, but also some detailed instantiation of the concept as it is depicted in a picture. A picture generally contains a greater amount of information about an object than does a word (e.g., the shape of a screwdriver's handle and its tip). Words, on the other hand, tend to evoke only the most generic properties of a concept. In the study of the cross-stimulus modality classification described earlier (Shinkareva et al., 2011), the classification accuracy was higher when the classifier was trained on word-cued activation and tested on pictures, versus when it was trained on pictures and tested on words. This result suggests that although the neural representations of words and pictures are similar to each other, pictures activate additional information that is specific to the picture. The classifier that was trained on pictures and tested on words apparently extracted some information unique to the pictures, leading to a classification accuracy that was lower than when the classifier was trained on words and extracted generic information common to the picture and word representations.

In sum, there is evidence of overlap in the semantic content between word- and picture-cued neural representations. However, additional research is needed to characterize the distinctions between the content of representations evoked by words versus pictures. Can identical representations be evoked between words and pictures by manipulating the information that is directly expressed in either presentation modality? For example, would the addition of modifiers to a word increase the amount of information about the evoked concept (e.g. "short, yellow Phillips screwdriver")? Similarly, can the neural representation of a concept evoked by a picture be made more similar to the one evoked by a word by making the picture completely schematic, thereby removing the extra information conveyed by the picture? Empirical studies that address such issues would enable a refinement of theories of how concept knowledge is neurally stored and activated (e.g., dual-coding theory; Paivio, 1986).

Neural Representations of Lexical and Grammatical Categories

There has not yet been found a clear difference in activation patterns evoked by different word classes (e.g., verbs versus nouns). Studies that have addressed this question have been hampered by the problem that concepts corresponding to different grammatical categories are inherently different. For example, verbs are typically associated with concrete actions, whereas nouns typically refer to objects (see Vigliocco, Vinson, Druks, Barber, & Cappa, 2011, for a review of the brain activation underlying nouns and verbs). These grammatical categories also differ in terms of lexical stress and ortho-phonological typicality, which complicate matters further (Arciuli, McMahon, & de Zubicaray, 2012). Consequently, any differences in activation found between nouns and verbs might plausibly be attributed to differences in semantic content, rather than to (non-semantic) differences in lexical category or grammatical structure. One study compared the activation evoked by abstract nouns and verbs (e.g., "idea" versus "think") because abstract nouns and verbs are not associated with concrete objects or concrete actions and thus are not inherently different in the same way that concrete nouns and verbs are (Moseley & Pulvermüller, 2014). This study found no activation location difference between abstract verbs and nouns, whereas there was a difference between concrete verbs and nouns. The authors concluded that there are no word class-specific processing centers in the brain. However, the analysis focused on only a small set of regions of interest; a whole-brain comparison was not conducted, thus leaving the question open to additional investigation.

Other studies have reported differences in the activation locations evoked by pseudo-nouns versus pseudo-verbs (Shapiro et al., 2005). Pseudo-nouns (nonsense words with morphological cues to lexical category, such as ending in *–age*, cuing a noun) elicited greater activation than pseudo-verbs bilaterally in temporal regions, whereas pseudo-verbs (e.g., those ending in *–eve*) evoked greater activity in left-lateralized frontal areas. In another study, pseudo-verbs (e.g., ending in *–eve*) elicited greater activity in motor cortex than pseudo-nouns (de Zubicaray, Arciuli, & McMahon, 2013). Such differential activation evoked by stimuli that are devoid of meaning suggests that a word's lexical class is a possible dimension of lexical organization in the brain.

In a study using multivariate analysis, it was possible to distinguish between the activation patterns associated with semantically equivalent but grammatically different sentences (Allen, Pereira, Botvinick, & Goldberg, 2012). Specifically, a classifier could determine whether a sentence was ditransitive (e.g., "Mike brought a book to Chris") or dative (e.g., "Mike brought Chris a book"), despite the fact that the two grammatical constructions convey the same core information. The classifier used activation from left-lateralized brain areas involved in language processing, such as left inferior frontal gyrus. The result suggests that grammatical category is neurally represented independent of semantic meaning, but further research is needed that identifies the grammatical aspects of ditransitive and dative sentences that might be neurally represented. At the same time, it remains unclear whether grammatically different sentences with the same core meaning still have subtle differences in semantic content that can be detected in activation patterns.

If nouns and verbs tend to evoke differing semantic content (i.e., object- and action-related content, respectively), then some neurosemantic theories would posit that this content is primarily represented in association areas that integrate among different sensorimotor modalities, such as the anterior medial temporal lobe or angular gyrus (e.g., Patterson et al., 2007; for a review of these and other theories, see Mahon & Caramazza, 2008; Meteyard et al., 2010; and Kiefer & Pulvermüller, 2012). In support of this view, abnormal functioning of these brain regions is associated with impairments to semantic processing, but not to the performance of non-semantic cognitive tasks (e.g., Pobric et al., 2007). Because many of the activation differences observed between nouns and verbs are *not* constrained to these association areas, these theories might predict that activation differences between lexical categories could instead reflect non-conceptual linguistic processing. For example, greater activity observed in motor cortex in response to verbs versus nouns could reflect verb-specific ortho-phonological properties (de Zubicaray et al., 2013). However, there is also reason to believe that sensorimotor activation elicited by words instantiates the concepts to which the words refer, which may constitute a form of semantic processing (Mahon & Caramazza, 2008). Thus, additional research that demarcates the semantic system in the brain may provide some answers regarding which brain areas underlie syntactic processing.

Finally, another prominent question addressed by the neurosemantic approach is whether neural concept representations differ between different languages, assuming that the words or phrases are good translation equivalents of each other. There is suggestive evidence that the neural representation of a concept is largely the same, regardless of which language is used to evoke it. In two neurosemantic studies of bilinguals, it was possible to identify the activation pattern associated with an object concept cued in one language based on the activation pattern of the same concept denoted in another language (Buchweitz, Shinkareva, Mason, Mitchell, & Just, 2012; Correia et al., 2014). However, there are subtle clues that neural representations of word classes differ between speakers of different languages due to differences in the semantic content associated with the classes. For example, the most frequently used class of verbs in Spanish refers to the *path* of an object (see Goldstone & Kersten, 2003), whereas English verbs often refer to the manner of an object's *motion*. Thus, neural concept representations might differ between the two languages in this respect, despite a core commonality in the representations.

Commonality of Neural Concept Representations across Different Individuals

One of the most dramatic findings in neurosemantics is that the fine-grained activation pattern corresponding to a given concept is largely common across people. When two people think about the concept *apple*, their activation patterns are distributed over the same brain locations and are very similar. When a classifier is trained on the activation patterns from a set of participants (whose activation data were spatially aligned to a common anatomical template), it can reliably predict which concept a left-out test participant is contemplating. This phenomenon of commonality has been demonstrated for the neural representations of concrete objects (Just et al., 2010), emotions (Kassam et al., 2013), numbers (Damarla & Just, 2013), and social interactions (Just et al., 2014).

The ability to accurately classify concepts across people suggests that some of the same properties of a given concept are evoked in many or most individuals. Behavioral studies in which participants generate properties of objects report that there are some properties that are commonly associated with a given object concept (e.g., Cree & McRae, 2003; Nelson, McEvoy, & Schreiber, 1998). Moreover, a neurosemantic study uncovered suggestive evidence that the most defining properties of a concept are automatically activated during any instance of evoking that concept, even during tasks for which that information is irrelevant (Hsu, Schlichting, & Thompson-Schill, 2014).

Accurate cross-individual classification is somewhat surprising given the uniqueness and variety of personal experiences and associations that might underlie a concept, in addition to the varied levels of experience with a concept. Although the commonality of neural representations of concepts has been demonstrated, the unique aspects of neural representations have yet to be characterized. The unique components could be similar in kind to the common aspects (which constitute semantic memory), or they could be tagged in some way as part of one's autobiographical memory (Charest, Kievit, Schmitz, Deca, & Kriegeskorte, 2014). It will be interesting to determine the characteristics of concept knowledge that are unique, although to do so will be challenging precisely because any emerging pattern of results will be difficult to aggregate over participants. If successful, such research may enable an understanding of how different properties of a neural representation, such as its particular pattern of activity or its anatomical distribution, are shaped by individual factors (e.g., unique experience, genetic predisposition) versus shared, cross-individual factors (e.g., cultural values, evolutionarily conserved biases toward processing certain types of information, and inherent neural constraints; Sadtler et al., 2014). Representational commonality might indicate that there exist category-specific brain networks that process specific kinds of information that are important to survival, such as information about food or shelter (Mahon & Caramazza, 2003).

Methods That Assess Representational Commonality by Abstracting Away from Person-Specific Patterns of Neural Activity

There is another approach that makes it possible to compare neural representations across people, namely cross-individual comparison of the similarity relations among the concepts' activation patterns (Raizada & Connolly, 2012). This approach uses RSA (described earlier) to abstract the activation data away from voxel space (i.e., activation patterns corresponding to different brain locations) to representational similarity space (i.e., correlations among the activation patterns). Thus, the method does not need to warp different participants' activations to a common anatomical template. Classification is not performed directly on the activation patterns. Rather, the classifier determines whether the similarity relations among the concepts' activation patterns are similar across individuals. Cross-individual classification in representational similarity space may produce greater classification accuracy because the method does not need to account for individual differences in brain anatomy. Thus, although there may be slight differences in the precise brain locations of two participants' representations of the same concept, the neural similarity between the two representations is robust to these differences.

Another cross-individual classification method is the mapping of each individual's activation data from original voxel space to a common, high-dimensional space over all the participants (Haxby et al., 2011; Haxby, Connolly, & Guntupalli, 2014). The dimensions in this new common space are not individual voxels, but rather distinct response-tuning functions defined by their commonality across the different brains. This method also results in greater cross-individual classification accuracy.

Yet another cross-individual classification method encodes both activation location and magnitude in a graph structure and is robust to anatomical differences among people (Takerkart, Auzias, Thirion, & Ralaivola, 2014). Thus, the warping of activation data to align with a common anatomical template might lead to an underestimation of the commonality of the semantic content in neural representations.

Intriguingly, one study that used RSA assessed commonality of neural representations between human beings and macaque monkeys (Kriegeskorte, Mur, Ruff, et al., 2008; Kriegeskorte, 2009). This study indicated that pictures of various animate and inanimate objects elicited activity patterns that had similar representational similarity between the humans and monkeys in homologous inferotemporal cortex, a set of high-order visual brain areas. The human data consisted of fMRI activation, and the monkey data were single-neuron electrophysiological recordings from two macaque monkeys (Kiani, Esteky, Mirpour, & Tanaka, 2007). The commonality between the neural representations belonging to the two species is illustrated in Figure 21.4. To the extent that the inferotemporal activation reflected semantic processing rather than perceptual processing of the picture stimuli themselves, this result may bear on the profound question of the nature of thought in other species. The result also motivates future research that uses similar methods to compare neural representations between humans and monkeys within other brain areas, and for other concept categories such as numbers (e.g., Beran, Johnson-Pynn, & Ready, 2011).

Neural Representations of Abstract and Concrete Concepts

Previous behavioral research suggests that how a concept is stored and otherwise processed depends on how concrete or abstract it is. For example, words that refer to concrete concepts (e.g., "ball") are more quickly recognized (e.g., Schwanenflugel & Harnishfeger, 1988), and knowledge of concrete concepts is more resistant to brain damage (see Coltheart, Patterson, & Marshall, 1980). Several fMRI studies have shown that words that refer to either abstract concepts (e.g., "blame") or concrete concepts activate overlapping but partially distinct brain networks, with abstract concepts eliciting greater activation in the frontal language system (e.g., Binder, Westbury, McKiernan, Possing, & Medler, 2005; Friederici, Opitz, & von Cramon, 2000; Noppeney & Price, 2004). In several studies, abstract words were defined as those with low imageability and concreteness ratings, and vice versa for the concrete words. The overlapping portion of activation between the two word classes consisted of left-lateralized areas that

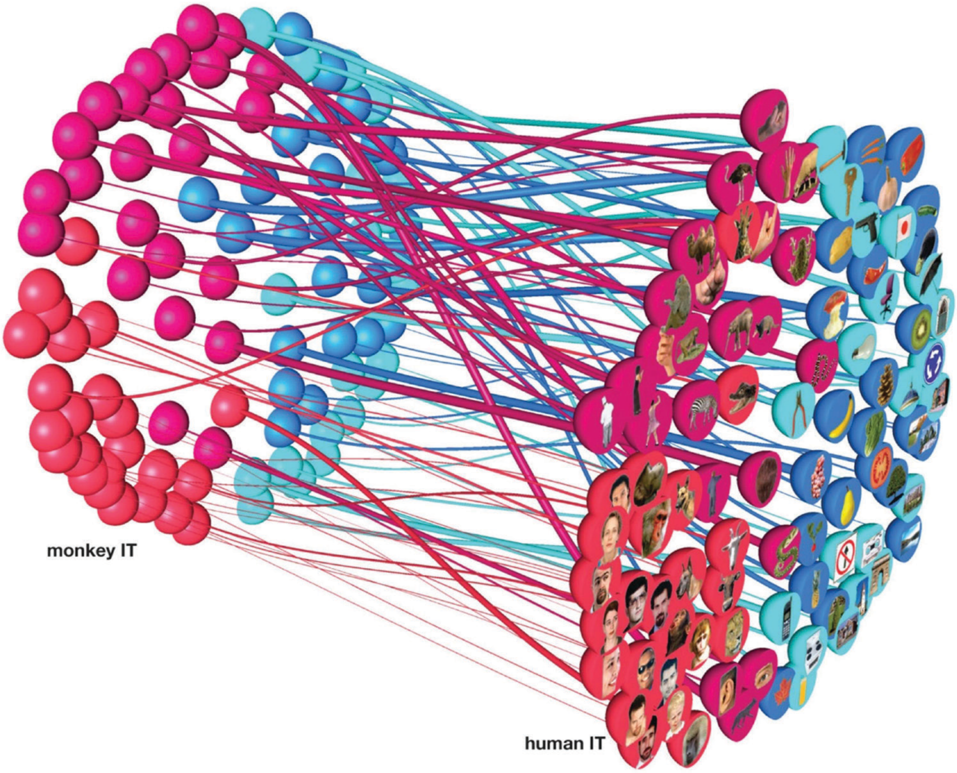

FIGURE 21.4. Neural representations of concrete objects are similar between monkeys and humans. Arrangements of the same picture stimuli separately for monkeys and humans, such that the distance between any two pictures reflects the dissimilarity between their activity patterns (1 – the spatial correlation) in IT (inferotemporal cortex), a set of high-order visual brain areas.

Monkey data: 674 single-neuron electrophysiological recordings from two macaque monkeys (Kiani et al., 2007). Human data: fMRI activation in 316 voxels (Kriegeskorte, Mur, Ruff, et al., 2008). Different categories: face (red), body (magenta), natural object (blue), artificial object (cyan). The lines connect the same pictures between monkey and human; thick lines indicate that the neural representations were dissimilar between monkey and human.

Source: The figure was adapted from Kriegeskorte (2009) freely under the terms of the Creative Commons Attribution License.

receive inputs from multiple sensory modalities, such as angular gyrus. In one of the studies, concrete concepts, in contrast to abstract concepts, elicited greater activation in right-lateralized multimodal areas (Binder et al., 2005). Abstract concepts produced greater activation primarily in left inferior frontal gyrus, an important area in the language system. Thus, the findings from these univariate analysis-based studies suggest that abstract (versus concrete) concepts evoke other verbal concepts and involve less sensorimotor knowledge than concrete concepts.

The only multivariate analysis-based study to date that compares the neural representations between abstract and concrete concepts documented findings similar to those of the univariate analysis-based studies (Wang, Baucom, & Shinkareva, 2013). For example, left inferior frontal gyrus was among a small set of regions that by itself enabled a classifier to recognize the activation patterns corresponding to abstract concepts. Taken together, the results in this research area support the dual-coding theory of semantic processing (Paivio, 1986), which postulates that abstract concepts are neurally represented primarily as lexical items, whereas concrete concepts are additionally stored as sensorimotor representations.

The findings of left inferior gyrus involvement in the representation of abstract concepts leave open the question of what type of information is represented there. Apart from its critical role in language processing, this region has been associated with phonological working memory (Burton, 2001), and so activation patterns detected in this region might contain sustained phonological representations of words, while knowledge related to the word meaning is being retrieved from other brain locations. Left inferior frontal gyrus has also been suggested to mediate conflicts in the retrieval of knowledge among competing alternatives (Thompson-Schill, D'Esposito, & Kan, 1999). Thus, activation detected in this region might reflect various instances of mediation among competing requests for the retrieval of knowledge related to the concept currently being thought about. According to either interpretation, activation patterns in this region would not appear to encode the knowledge per se associated with a concept.

The evidence uncovered thus far suggests that an abstract concept evokes a set of verbal or lexical representations associated with that concept, more so than does a concrete concept. This lexical information might also include concrete words, whose meaning is neurally represented in sensorimotor brain areas. Regression models might be used to discover sensorimotor activation patterns associated with abstract concepts by accounting for any hidden concrete factors that underpin the representations.

Scientific concepts are a specific type of abstract concept learned only through formal education. The neural signatures of scientific abstract physics concepts (e.g., *gravity, torque, frequency*) can be decomposed into meaningful underlying neural and semantic dimensions, despite their abstractness. Mason and Just (2016) used factor analysis to uncover the underlying dimensions of the neural representation of 30 physics concepts. The four main dimensions underlying the neural representation of these abstract concepts were *causality, periodicity, algebraic representation* (a sentence-like statement of the quantitative relations among concepts), and *energy flow*, all of which are dimensions that are used for representing familiar concrete concepts. For example, a concept like *frequency* has a strong *periodicity* component. (The brain locations corresponding to this factor included bilateral superior parietal gyrus, left postcentral sulcus, left posterior superior frontal gyrus, and bilateral inferior temporal gyrus.) The applicability of these underlying dimensions was assessed in terms of a classification model that used the factor-related brain locations to accurately classify the 30 abstract concepts based on their neural signature. The findings suggest that abstract scientific concepts are represented by repurposing neural structures that originally evolved for more general purposes. The underlying brain capabilities that form the basis for physics concepts existed long before physics knowledge was developed.

CHANGES IN NEURAL CONCEPT REPRESENTATIONS WITH LEARNING

The ability to track the growth of a neural concept representation speaks to one of the foundational goals of cognitive neuroscience research, namely to understand the neural basis of knowledge acquisition. The study of concept learning also promises to enable a greater understanding of how concept knowledge is represented and processed in the brain. However, little is known about the changes that occur in a neural concept representation as a new concept is being learned.

Much of the existing research on concept learning has focused on changes in which brain regions show heightened activation between pre- and post-learning. For example, after a session of learning how to manipulate novel tool-like objects, activation to pictures of the objects was found to shift predominantly to motor cortex compared to pre-learning (Weisberg, van Turennout, & Martin, 2007). Another study showed that after participants were verbally instructed about the kind of motion or sound that was associated with novel living objects, the activation elicited by the object pictures was localized to motion-specific or auditory cortex (James & Gauthier, 2003). These studies showed that the brain regions that became active after learning corresponded to the kinds of information that were taught. However, the univariate analyses used in these studies did not permit a determination of how each individual new concept became encoded in a distributed neural representation within the new sites of activation.

A multivariate study of concept learning documented the emergence of the neural representations of individual new concepts (Bauer & Just, 2015). Specifically, the growth of the representations of new animal concepts was monitored as two properties of each animal were taught, namely an animal's habitat and its diet or eating habits. The learning of information about each of these dimensions was demonstrated by an increase in the accuracy of classifying the animal identities based on the brain areas associated with the dimension that had been learned. For example, after participants had learned about the habitats of some animals, it was possible to classify which animal they were thinking about by training a classifier on the activation patterns in regions associated with shelter information. This study provides a novel form of causal evidence that newly acquired knowledge comes to reside in the brain regions previously shown to underlie a particular type of concept knowledge.

Another neurosemantic study examined the changes in the neural representations of complex mechanical concepts as they were being learned, and found that different stages of learning are associated with different sets of brain regions that encode the emerging knowledge (Mason & Just, 2015). Specifically, the study demonstrated how incremental instruction about the workings of several mechanical concepts (e.g., bathroom scale, automobile braking system) gradually changed the neural representations of the systems. The representations progressed through different states that reflected different learning stages, starting with the visual properties of the concept encoded from the display, mental animation of mechanical components, generation of causal hypotheses associated with the animation, and determination of how a person would interact with the mechanical system. Research on intermediate stages of learning has lagged behind studies that focus only on final outcomes of learning (Karuza, Emberson, & Aslin, 2014). The results in Mason and Just (2015) raise the possibility that the neural representations of familiar concepts (which is the only type of concept that most previous studies have investigated) may fail to reveal the constructive processes by which the neural representations become established. The constructive processes may reveal some fundamental properties of neural concept representations.

The neurosemantic research on concept learning provides a foundation for brain research to trace how new knowledge makes its way from the words and graphics used to teach it, to a neural concept representation in a learner's brain. It might foreshadow an era in which brain imaging and neurosemantic methods are used to diagnose which aspects of a concept a student misunderstands or lacks, in a way that might be more fundamental and accurate than conventional behavioral testing. An fMRI study in which real-time measurement of brain activation identified mental states that were either "prepared" or "unprepared" for encoding a new stimulus lends credence to this possibility (Yoo et al., 2012).

The study of how the learning process changes neural concept representations promises to enable a greater understanding of the kinds of information encoded in neural representations. Just as neurosemantic methods have been useful in determining where and how the different dimensions of a concept are encoded, these methods might eventually be used to track the developmental trajectory of neural representations as a function of various factors of interest, such as a person's previous experience or knowledge, or elapsed time between learning episodes. Perhaps a comparison of representations at different stages of knowledge expertise would aid in deciphering the kinds of information that are encoded in the representations. For example, chess experts can remember large configurations of chess pieces on a board by representing various relationships among the chess pieces (Gobet & Simon, 1996). Comparisons between the information that is neurally encoded in a domain expert versus a novice might illuminate the process of building complex neural representations.

Conclusion

Neurosemantic methods have enabled enormous advances in uncovering how various types of concept knowledge are neurally represented, and also in characterizing the information contained in the representations. The ability to study how different concepts are neurally represented has only recently become possible since the development of data analytic methods that can detect a correspondence between a distributed activation pattern and an individual concept. The key virtues of the neurosemantic approach over older methods are that it generally permits greater sensitivity to uncovering the underlying phenomenon, and it adheres to the fundamental principle that concept information is encoded in neural populations distributed throughout the brain. The approach promises to illuminate a number of prominent questions; for example, the field is better equipped to determine whether abstract concepts are neurally encoded as lexical representations, or whether abstract thoughts are underpinned by sensorimotor factors as revealed by organized patterns of activation in these brain regions. The neurosemantic paradigm provides the tools for forging discoveries in areas of daunting complexity, such as how the relations among a concept's underlying semantic dimensions are neurally encoded and thereby represent a cohesive concept, and how learning establishes and shapes new representations.

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CHAPTER 22

FINDING CONCEPTS IN BRAIN PATTERNS

From Feature Lists to Similarity Spaces

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INTRODUCTION

One likes to believe that the methods used by scientists are determined by the questions that they aim to answer, and not the other way around. However, there are instances when one can see that the development of a new method has had the effect of changing the questions that are asked of it, and in so doing, changes the course of scientific inquiry. This chapter reviews one such change of course. The story begins with the advent of cognitive neuroimaging, and with a methodological insight by Michael Posner and his colleagues at Washington University. Posner realized that the very same logic of "cognitive subtraction"—which could be used to isolate a single mental operation (by comparing reaction times to two tasks that differed only by the presence of absence of that operation; Posner, 1978)—could also be applied to isolate the neural correlates of a single mental event (by comparing brain images; Posner, Petersen, Fox, & Raichle, 1988; see Heim & Specht, Chapter 4 in this volume). This insight arguably created the field of cognitive neuroimaging—a field that immediately began to yield insights into the ways in which any complex cognitive system could be carved into parts. One such system was semantic memory, and the subtractive approach allowed cognitive neuroscientists to identify regions of cortex whose activity increased or decreased as a function of which "part" of the concept was isolated. In the years that followed, the study of concepts became the study of concept-parts (i.e., features), the importance of which was confirmed by activation difference maps. This shift likely surprised cognitive psychologists who had witnessed a move *away* from thinking of concepts as feature lists, prior to the advent of functional neuroimaging. However, the method of image subtraction was well suited to questions about parts. Fast forward from 1988 to 2001, when an analysis of functional magnetic resonance imaging (fMRI) data that was not based on image subtraction shook up the world of cognitive neuroscience: Haxby et al. (2001) described a methodology for characterizing what was called in their abstract a "pattern of response," and discussions of neural patterns have permeated all areas of cognitive neuroscience ever since. Perhaps nowhere has the consequence of this innovation been as impactful as in the study of concepts, which increasingly are described by their patterns and not by their parts. In this chapter, we review studies of conceptual knowledge that illustrate this course correction, and we describe some of the challenges that lay ahead. But first, we review some foundational principles about concepts and provide a brief tutorial into the methodology—generally called multi-voxel pattern analysis—that changes the way concepts are studied today.

What Is an Object Concept?

How is it that we are able to recognize and interact with things in the world that we have never encountered before? Although we come across many novel objects throughout our lives, they often resemble other things that we already know about. If we have developed a concept (a mental representation) that corresponds to a category of objects (a class of things in the world that elicit a common response), then our knowledge of the concept will allow us to identify and appropriately respond to new instance of that category (Murphy, 2002). For instance, we can figure out whether or not a newly encountered object is a spoon by asking ourselves whether this new thing is similar to our concept of *spoon*. If the object resembles the concept, then we can infer its identity and its properties, and use it to eat our soup. In this way, concepts serve as information structures that link our abstract, accumulated knowledge about various things in the world to our present, novel interactions. The speed and ease with which we can identify new instances of familiar objects belies the complexity and impressiveness of this cognitive phenomenon (see Garcea & Mahon, Chapter 23 in this volume).

Inferring Concepts via Similarities

Our concepts contain much of our world knowledge, as they allow us to infer the identity of each unique entity that we encounter. Does this new item resemble something we have seen before? To accomplish this feat, concepts must be broad enough to abstract over some variation in object properties because not all instances of a concept will have the exact same characteristics, yet narrow enough that new entities are not mistakenly classified, and different sorts of objects can be discriminated from one another (e.g., a fork versus a spoon). Hence, some variation in object properties is tolerated (e.g., a spoon can be made of plastic or metal), yet other variation is not (e.g., a rounded end versus a pronged end).

How do we determine which features of a concept are free to vary, and which are the defining characteristics of that concept? Given the enormous amount of complexity and variation in the world, it is overly simplistic, if not impossible, to define concepts by a finite set of necessary and sufficient features. In fact, the philosopher Wittgenstein proposed that concepts cannot be defined by specific features, but rather by "family resemblances," that is, sets of overlapping similarities between members of a category (Wittgenstein & Anscombe, 1953). Objects in a category resemble other category members more than non-members, and instances of a concept are relatively more similar to one another than they are to instances of other concepts. This theoretical framework has long provided a useful approach for studying categorization in the domains of both cognitive psychology (e.g., prototype and exemplar theories) and cognitive science (e.g., applications in artificial intelligence).

As rich information structures, concepts allow us to generalize and discriminate among similar entities. One way, therefore, to understand the nature of these information structures is to characterize the similarity (and dissimilarity) between concepts. However, in studying the neural representation of concepts, neuroscientists have only recently started to adopt similarity-based approaches (see Bauer & Just, Chapter 21 in this volume). Modern functional neuroimaging techniques have allowed neuroscientists to measure brain activity evoked by thoughts about concepts, rendered visible by fMRI. By studying the similarities among patterns evoked by various concepts, researchers can investigate how and where conceptual knowledge is represented in the brain. In this chapter, we will briefly describe how the neural similarities between mental representations of objects (i.e., object concepts) are computed from spatially distributed fMRI activity patterns. Then, we will review empirical findings that relate the observed neural similarities to various models of semantic representation. Using this approach, these studies have contributed to our understanding of how conceptual knowledge is stored and organized in the brain.

From Describing Features to Characterizing Similarities

Concepts endow us with the fundamental knowledge required to interact with all of the things that surround us. This information store comprises our semantic memory: a division of long-term, declarative memory, in which our knowledge about people, places, and things in the world is generalized and abstracted away from any specific experience, and is therefore considered conceptual in nature. How is this information organized, and which brain structures support this knowledge?

Feature-Based Models

One possibility is that concepts are organized by their respective properties. According to feature-based theories of semantic memory, the meanings of object concepts can be described as patterns of activation that are distributed over a concept's various visual and nonvisual features, like its shape and function (e.g., Allport, 1985; Barsalou, 1999; Tyler, Moss, Durrant-Peatfield, & Levy, 2000). These models predict that concepts that have similar features will have overlapping representations. Feature-based models also capture both category structure and within-category individuation because concepts from the same category will have overlapping features, yet each concept within a category is composed by its own unique set of properties.

Over the past few decades, most neuroimaging studies on concepts have focused on testing and finding support for these sorts of models. These reports have described the neural bases of concepts' features by identifying, for example, dissociations between neural activity associated with the visual versus nonvisual attributes of objects. For instance, Martin and colleagues (1995) found that retrieval of action-related information about a concept is associated with activation in middle temporal and frontal cortex, whereas retrieving color knowledge about a concept activates bilateral ventral temporal cortex (VTC) (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995). Since this report, several other studies have found that retrieving information about different object attributes (e.g., shape; color; motion) activates distinct and spatially distributed cortical areas (for a review, see Martin, 2007; Thompson-Schill, 2003).

While fMRI studies of object knowledge offer support for a feature-based organization of object concepts, they have mostly constrained their inquiries to descriptions of the conditions under which neural activity increases during conceptual knowledge retrieval. Such comparisons can reveal the stimulus and task conditions that give rise to dissociable patterns in brain activity. However, this research has not fully characterized the representation of information within these activated regions.

Moreover, on theoretical grounds, descriptions of neural activity associated with various object properties can contribute only part of the story of conceptual representation. After all, concepts are more than just sets of features. They are experienced as wholes, such that their properties combine and interact to jointly represent a coherent entity. In other words, concepts are more than the sum of their parts. Describing a concept's constituent features in isolation can offer only limited insight into how high-dimensional, information-rich concepts are represented. Instead, a more fruitful approach may be to investigate the relationships between whole concepts, and where and how these relationships are neurally represented. By characterizing the similarities between concepts and the similarities between their associated neural activity patterns, we can learn more about how concepts are structured in the brain.

Similarity-Based Models

One way to study the underlying neural structure is to measure the similarity between neural responses to objects that differ from one another along various stimulus dimensions. This approach is based on the premise that what we call a "representation" comprises representations of similarities (Edelman, 1998; Shepard & Chipman, 1970); that is, representations do not need to resemble the things that they represent—instead, what is important is that the representations preserve the similarity relations between the concepts that they represent.

With this approach, representations of concepts can be described in terms of the tuning parameters of the neurons that respond to a concept's various semantic features. These tuning properties can be inferred by measuring the similarity between concepts that share features. For example, a set of neurons that encode information about the concept *spoon* might evoke a similar response for a plastic spoon and a metal spoon, but a different response for a spoon versus a fork. Such neurons are tuned to (i.e., represent) specific object shape properties, but are not sensitive to differences in the objects' materials. Beyond information about object shape and material, the high-dimensional representation of a concept such as *spoon* would also comprise several additional similarity spaces that reflect the concept's other properties. Each unique similarity space may be encoded in distinct (though perhaps overlapping) brain regions or networks, such that each similarity space could be described as one dimension of a more complete, high-dimensional representation.

In similarity models, data from direct (i.e., neural) and indirect (i.e., subjective, psychological) measurements are interpreted as proximity data that provide information about the distance between objects in an abstract, high-dimensional space. Concepts are encoded as points in this conceptual space, where the semantic similarity between the two concepts is measured by concepts' proximity to one another. In a high-dimensional space that represents knowledge about the shape of objects, the plastic spoon would be situated closer to the metal spoon, and farther from the fork. Additionally, one could conceive of another dimension of this high-dimensional space that represents knowledge of object materials, where a plastic spoon might be located closer to a plastic fork than it is to a metal spoon. By observing these similarity spaces, and the relative distances between different points in the space, one can infer the object properties that determine the relative arrangement of the points.

The standard method for computing a neural similarity space is to measure the activity evoked by each stimulus item (i.e., the response in a set of neurons while an experimental participant views a picture of a fork, or of a spoon), and then compute the similarity between the neural responses for each possible pair of stimulus items. The observed neural similarity space is then related to a model of semantic similarity space, where the similarity between every possible pair is again computed, but this time according to the concepts' predicted proximities. The predictions regarding the relative similarities among the stimuli come from a theoretical model of how the invoked concepts are semantically related (i.e., subjects' subjective ratings of the strength of similarity between *fork* and *spoon*). Here, the general question is whether concepts that are judged to be similar in the world, according to the model based on semantic relatedness, are represented by neural states that are likewise similar. With this method, one can test predictions against the data in a manner that abstracts away from the underlying representational substrate (that is, the stimulus attributes and the neural activity values, respectively).[1]

By comparing the neural similarity space to predicted models of the underlying semantic similarity space, researchers can identify where semantic content is encoded in the brain, generally, but also, more specifically, which components of semantic knowledge are reflected in different neural similarity spaces. In this way, the neural similarity space is observed and then compared to semantic models of the space that would be predicted if a region were sensitive to a specific type of conceptual information. For instance, does an observed neural similarity space correspond to the visual features of the concepts, or more abstract semantic properties?

Note that the preceding approach describes a hypothesis-driven similarity analysis, where neural similarities are compared to a predicted model of similarity. However, instead of testing the correspondence between the neural similarity space and a predicted similarity space, one could directly extract the dimensions of a neural similarity space and infer the type of information that it carries, unconstrained by the theoretical assumptions of any specific model. In this data-driven approach, exploratory visualizations are used to discover natural groupings between concepts in the neural similarity space. This could be accomplished with a variety of exploratory analytic techniques, which we will describe in later sections.

Computing Neural Similarity Spaces with MVPA: A Brief Tutorial

Most neural similarity analyses typically begin with the same preprocessing and estimation of hemodynamic activity performed in traditional univariate methods. A pattern of activation for a given stimulus item is then identified as a vector of activity values, equal to the length of the number of voxels selected for analysis. The voxels included in this vector can be selected from a variety of criteria, including anatomical and functional constraints in a specific regions of interest (ROIs). In more exploratory analyses, multivoxel patterns are measured and compared in roaming "searchlights," which are local neighborhoods of spatially contiguous voxels iteratively sampled throughout the brain (Kriegeskorte, Goebel, & Bandettini, 2006).

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[1] The versatility in this method can also be leveraged to compare similarity spaces from brain data measured with different neuroimaging techniques (e.g., the representational structure derived from fMRI data versus magnetoencephalography data) (cf. Cichy et al., 2016).

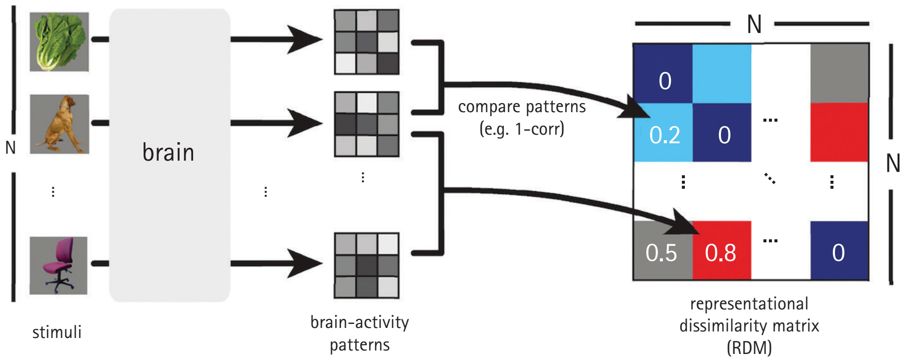

FIGURE 22.1. In similarity-based fMRI analyses, researchers expose subjects to a set of *N* stimulus objects, each presented in isolation. Multi-voxel patterns of neural activity evoked by each stimulus are measured in the same set of spatially distributed voxels. Each of these multi-voxel patterns are then compared to one another. The computed similarity value is entered into a matrix, where the value assigned to a matrix cell indicates the similarity between the pair of stimuli, which corresponds to objects which label that row and column.

Source: From Nili et al. (2014). Reprinted with permission from the Creative Commons Attribution License.

Neural similarity between two patterns evoked by two different stimuli can be computed using measures of vector proximity (e.g., Pearson or Spearman correlation; cosine similarity; Euclidean distance) or linear separability (cf. Weber, Thompson-Schill, Osherson, Haxby, & Parsons, 2009). The magnitude of similarities measured between every possible pairing is often illustrated as a matrix, in which the experimental stimuli are indexed horizontally and vertically. Each cell of the matrix contains a similarity value, which compares the two multi-voxel patterns associated with the stimuli that label that row and column (Figure 22.1). By computing neural similarity spaces, researchers can examine the relative similarities and dissimilarities in the neural activity patterns evoked by the experimental stimuli. In the following sections, we will discuss examples in which neuroscientists have utilized this approach to probe the neural bases of conceptual representations.

HOW DOES THE INFORMATIONAL SPECIFICITY OF CONCEPTS VARY ACROSS BRAIN REGIONS?

In order for us to flexibly use our concepts, they must be represented at varying levels of abstraction. Objects contain a wealth of information, and a set of objects can be relatively similar or dissimilar to one another, depending on the features by which they are being compared. For example, a beetle and a moth have distinct visual characteristics that allow us to distinguish between them, but they are also similar to each other in many ways, and hence are both grouped into the category *insects*.

Which brain regions represent various object dimensions and their varying levels of specificity? In other words, which areas of the brain are sensitive to higher-order, cross-category distinctions between concepts, versus item-specific, within-category distinctions? To study the similarity spaces of concepts, researchers have varied the relative degrees of specificity and abstractness between object stimuli. We begin this section by describing various models of similarity that predict how concepts are represented in the brain, and by summarizing the neural evidence in support of each of these models.

Discrete Models of Similarity Spaces

One straightforward similarity-based model of semantic representation predicts a category-level organization of concepts. According to this model, objects from the same category should be similar to one another, while objects from two different categories should be dissimilar. To construct these models, researchers have relied upon predefined semantic categories based on conventional groupings of objects. The categories could be broad, superordinate classifications (e.g., *animals*) or subordinate groupings (e.g., *cats*). An example of a category-based model of similarity is depicted in matrix form in Figure 22.2. To identify brain areas where neural responses are predicted by this

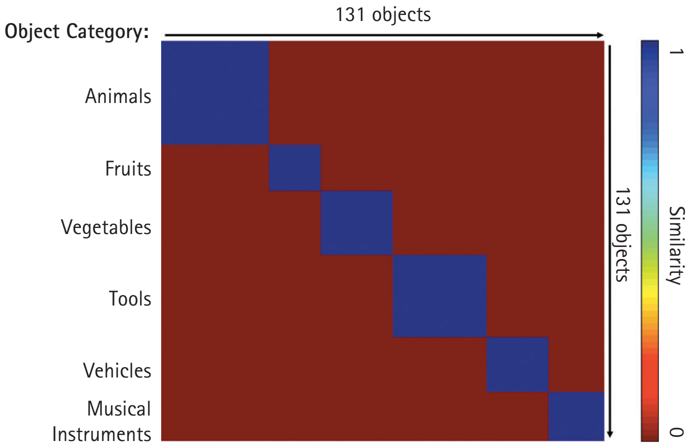

FIGURE 22.2. A model of discrete category-level similarity, similar to the model employed in Clarke and Tyler (2014). The stimulus objects are indexed in the same order along the rows and columns of the matrix. The color bar to the right indicates the degree of similarity indicated by each color label, where pairings in blue indicate maximal similarity and pairings in red indicate maximal dissimilarity. In this model, all objects within a category are predicted to evoke similar activity patterns, and all comparisons of objects from two different categories are predicted to exhibit dissimilar activity patterns. Note that the predicted patterns are symmetric and redundant on either side of the diagonal because the predicted similarity between two objects is symmetric (e.g., the similarity between object 1 and object 2 is equal to the similarity of object 2 versus object 1).

sort of model, researchers have measured the multi-voxel patterns evoked by pictures of various real-world objects that span a number of object categories. A similarity matrix is then constructed, to compare the pairwise similarity between responses evoked by each possible pairing of two objects from the same category, versus the neural responses evoked by pairs of two objects from two different categories.

Using this approach, researchers have found that neural activity in posterior and ventral regions of temporal cortex (VTC) exhibit this coarse level of category-based similarity. For example, Haxby et al. (2001) found that in object-selective regions of VTC and ventrolateral occipital cortex, patterns evoked by the same subordinate object class (e.g., one shoe versus another shoe) more frequently exhibited greater similarity, relative to patterns evoked between categories (e.g., a shoe versus a bottle). Additionally, Clarke and Tyler (2014) found that searchlight volumes in lateral occipital cortex (LOC), posterior VTC (pVTC), and left perirhinal cortex exhibit more similar neural responses for objects from the same superordinate category, relative to noncategory members. In addition to category-level distinctions, Clarke and Tyler found that a model based on domains of object animacy (nonbiological—plant—animal) predicted neural similarity spaces in bilateral medial pVTC and right lateral pVTC. Taken together, these findings indicate that subregions of VTC encode coarse distinctions between predefined object classifications.

Continuous Measures of Similarity Spaces

Instead of comparing neural responses evoked by traditionally defined object categories, it may be more informative to examine the neural similarity spaces evoked by individual concepts, both within and between object categories. To characterize finer-grained distinctions between real-world objects, researchers have begun to study the item-specific signals within distributed patterns of neural activity. These studies employ parametric analyses of similarity, where neural responses are related to descriptions of a stimulus space that is more detailed and continuous than binary category membership assignment.

The similarities between stimulus items can be measured with a variety of methods. The main division is between hypothesis-driven versus data-driven similarity analyses. In hypothesis-driven approaches, the data are used to test predefined, theoretically motivated predictions. In contrast, in data-driven approaches, the results reflect the data. The former method allows one to *test* specific models of similarity, whereas the latter approach allows one to *discover* the similarities that are present in the neural data. Below, we review the applications of each of these methods.

In VTC, a common pattern of results in emerges from these two types of analyses. Several studies have identified a gradient of informational specificity in ventral brain regions, whereby responses in more anterior regions increasingly reflect sensitivity to higher-level and item-specific properties, such as object shape and category, while more posterior regions in early visual cortex (EVC) are sensitive to lower-level visual properties. The functional and anatomical dissociations between the neural similarity spaces that are predicted by these divergent models indicate that different brain regions are sensitive to different variations across stimulus features.

Predicting Item-Level Similarities

One way to investigate finer-grained, within-category similarity spaces is to compare item-level neural similarity spaces to models that are based on continuous, rather than categorical, dimensions. These models are constructed according to what one would predict the similarity space would look like if it were sensitive to graded variations among stimulus items.

To construct a model of item-level semantic similarity, researchers often rely upon explicit, subjective assessments of the pairwise similarities between two stimuli. To collect these judgments, researchers instruct participants to report the relative similarity between each possible pairing of the experimental stimuli. Researchers then use these models to examine, for example, whether participants' judgments of the similarity between a bear and a zebra correspond to the similarity of their respective neural activity patterns. Weber and colleagues (2009) used this approach to examine conceptual similarity among various mammals (e.g., camels, hippos). The pairwise similarities between the multi-voxel patterns evoked by mammal pictures were correlated with participants' post-scan, pairwise rankings of conceptual similarity for the same set of mammals. Neural similarity and the behavioral similarity measures were correlated in object-selective functional regions of interest (fROIs) in bilateral LOC. In a similar study, Connolly et al. (2012) examined the neural similarity space evoked by exemplars from a wider range of animals. This study compared the neural responses evoked by six animal species, from three biological classes (primates, birds, and insects). Participants' subjective similarity ratings predicted the neural similarity spaces in searchlight clusters centered in bilateral LOC. Moreover, in both of these studies, the neural similarity spaces observed in EVC did not match the subjective similarity ratings.

In contrast, the neural similarity spaces in EVC are sensitive to lower-level visual features. Researchers develop image-based models of similarity, which are independent of semantic information like object identity or category membership. These image-based models are typically constructed by computing the pixel-wise similarity between stimulus pictures (e.g., Weber et al., 2009) or by comparing the stimulus pictures with a set of spatial filters and then simulating the responses of V1 complex cortical cells (e.g., Connolly et al., 2012; Clarke & Tyler, 2014; cf. Serre, Wolf, Bileschi, Riesenhuber, & Poggio, 2007). Importantly, these low-level, image-based models predict the neural similarity spaces observed in EVC, but not VTC or LOC. These findings indicate an anatomical dissociation between more posterior, early visual regions, which are sensitive to visual similarities like luminance and line orientation, and progressively anterior regions in VTC and LOC, which correspond to subjective ratings of similarities between pictures of objects.

Discovering Item-Level Similarities

Instead of comparing neural similarity spaces to predicted models, researchers have also used exploratory, data-driven methods, such as multidimensional scaling (MDS) and hierarchical clustering, to project higher-dimensional similarity spaces onto a more visualizable, lower-dimension space. Researchers use these techniques to visualize the similarities that emerge in a particular brain region, and to discover the aspects of representational space that a given region encodes. Rather than testing hypotheses about specific patterns in the neural data, this approach allows researchers to look for interpretable relationships that are present within the observed neural patterns. Results from these sorts of analyses have largely conformed to the findings from hypothesis-based approaches, although they have extended some results as well.

Using data-driven analyses, Kriegeskorte and colleagues (2008) found that neural similarity patterns in object-selective VTC generally conformed to conventional human categories. Here, the authors measured the multi-voxel patterns evoked by 92 real-world objects, and then used hierarchical clustering methods and MDS to interpret patterns in the resulting neural similarity space. The resulting clusters of objects revealed a broad distinction between neural patterns evoked by animate and inanimate objects, as well as more fine-grained distinctions within categories, where faces and body parts formed sub-clusters within the animate objects (Figure 22.3). Moreover, models based on low- and intermediate-complexity stimulus features (e.g., luminance, silhouette) did

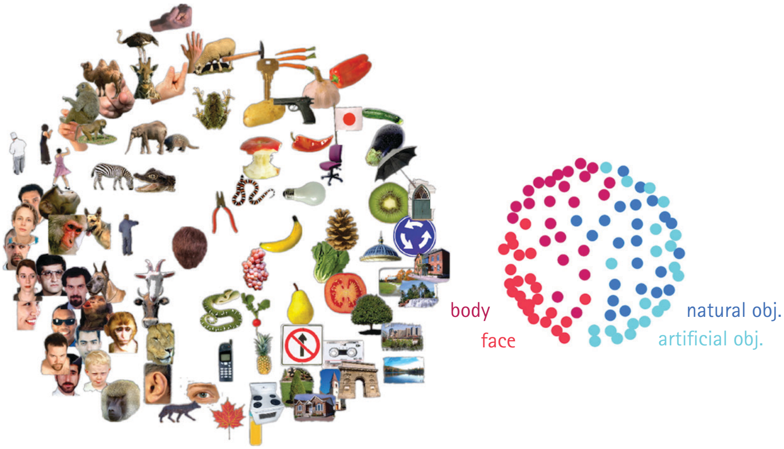

FIGURE 22.3. Data-driven, multidimensional scaling applied to neural similarity data extracted from human infero-temporal cortex in Kriegeskorte et al. (2008). The high-dimensional similarities between neural activity evoked by a variety of real-world objects are projected in two-dimensional space. This analysis reveals which objects tend to evoke more similar neural activity patterns. The similarity space on the right illustrates that assigning these stimuli labels based on their broad semantic category (e.g., body or face) reveals consistent distinctions between body parts and objects.

Source: Kriegeskorte et al. (2008). Reprinted with permission from Elsevier via RightsLink.

not account for the observed structure. In contrast, neural patterns in EVC exhibited weak category specificity, reflecting a broad distinction between animate and inanimate objects, but lacked the fine-grained distinctions within categories that were observed in VTC. This finding is consistent with a hierarchical organization in the ventral stream, where regions anterior to EVC code more complex stimulus features, such as object form and identity.

While Kriegeskorte et al. (2008) demonstrate how data-driven, bottom-up methods can be employed to study the brain's functional distinctions between broad categories, these methods have also enabled researchers to study finer distinctions between representations in greater detail. These analyses reveal differences in neural similarity spaces that were not well captured by similarity ratings. For example, in addition to their model-based analysis that compared neural activity patterns evoked by primates, birds, and insects, Connolly and colleagues (2012) also performed a cross-participant clustering analysis, such that the most similar neural similarity spaces across participants would cluster together. This analysis revealed the neural similarities observed in LOC were highly consistent across participants. In fact, the participants' neural similarity spaces in this region were more similar to one another than they were to the similarity space defined by pairwise similarity ratings of the stimuli, suggesting that the neural activity here reflects information that is not captured by the similarity model. Applying MDS to this region revealed that the most prominent dimension in LOC neural data reflected a continuum of animacy, where the most animate animals (primates) clustered at one end, and the least animate animals (bugs) clustered at the other end, with birds in-between the two. A follow-up study revealed a high degree of neural similarity between LOC activity patterns evoked by low-animacy animals (e.g., lobsters and ladybugs) and inanimate objects (e.g., tools and keys), despite the fact that participants' behavioral judgments reflected a dichotomous distinction between animate and inanimate objects (Sha et al., 2015). Although the LOC data did not quite conform with expectations of semantic structure according to the behavioral judgments, the complementary, data-driven analyses uncovered these compelling findings.

Perceptual or Semantic Similarity Spaces?

Which stimulus dimensions are driving the observed neural similarity spaces in ventral temporal regions? Relatedly, what sort of information does a participant rely upon to explicitly assess the similarity between two stimulus objects? These questions highlight the challenges in identifying the stimulus dimensions that underlie subjective ratings of semantic similarity, and relatedly, the stimulus dimensions that best predict the observed neural similarity space.

One possibility is that the subjective similarity ratings, and the corresponding neural patterns observed in VTC and LOC, are largely driven by visual effects. This possibility is supported by a couple of key points. For one, because the studies reviewed in the preceding sections presented concepts in pictorial format, the perceptual attributes of the concepts were more prominently featured than their nonvisual, more abstract properties. Additionally, while viewing these pictures in the scanner, participants were only required to retrieve minimal semantic information about the concept (e.g., exemplar naming in Clarke & Tyler, 2014; exemplar repetition detection in Weber et al., 2009), or no semantic information at all (e.g., detecting repetitions of stimulus pictures or a fixation cross, as in Haxby et al., 2001; Kriegeskorte et al., 2008; Connolly et al., 2012). Moreover, there is some evidence that these putatively within-category sensitive regions (i.e., LOC) also reflect subjective ratings of shape similarity for artificial shape stimuli, which presumably elicit minimal semantic information (Drucker & Aguirre, 2009; Op de Beeck, Torfs, & Wagemans, 2008).

Additionally, subjective assessments of pairwise similarity might also reflect the perceptual relatedness of the stimulus pictures. Weber and colleagues (2009) collected separate ratings based on their stimuli's conceptual similarity, biological similarity, and perceptual similarity. The judgments obtained according to these three dimensions were highly correlated with one another, such that it is not possible to determine the unique and relative contributions of each dimension for predicting the observed neural similarity structure. Likewise, in Connolly et al. (2012), participants rated the stimulus pictures based on their general similarity to one another, rather than according to explicitly semantic relationships. Here, too, the participants may have based their ratings on the perceptual similarity of the images, rather than semantic information about the concepts per se.

These methodological issues reflect the challenge in determining the extent to which the observed neural similarity spaces reflect both visual and nonvisual content, and the extent to which this information is conceptual in nature. One way to address this issue is to employ carefully controlled experimental stimuli, such that the dimensions of category membership and perceptual similarity are explicitly dissociated from one another; that is, stimuli must be equally perceptually similar to both category members and to noncategory members. In a fully crossed design, Bracci and Op de Beeck (2016) measured the neural similarities evoked by pictures of six different object categories (e.g., animals, minerals), where each category included an exemplar that had one of nine possible shape forms (e.g., roughly spherical, vertical oblong). In a similar approach, Proklova, Kaiser, & Peelen (2016) investigated the animate-inanimate distinction using pictorial stimuli where shape similarity was equated across the two object categories (e.g., a snake versus a rope). Such designs enable researchers to identify neural similarity spaces that correspond to the visual versus categorical (e.g., conceptual) distinctions among the tested stimuli. These studies revealed that shape and category information can independently and jointly contribute to neural similarity spaces throughout VTC. In the coming pages, we will discuss additional strategies that researchers have used to more directly target conceptual information about objects, independent of perceptual and non-semantic characteristics of the experimental stimuli.

Concepts as Feature Lists

To address some of the shortcomings of subjective similarity judgments, researchers have constructed alternative models of item-level similarity. For example, one could first catalog the visual and nonvisual semantic features that are typically associated with each concept. Then, the list of features for each concept could be compared to one another, to assess how well the two concepts align on their various features. This approach allows researchers to characterize meaningful dimensions that are not well captured by explicit similarity judgments of picture stimuli (i.e., more abstract and nonvisual features).

To construct these models, researchers first collect feature-norming data. In these tasks, behavioral participants are presented with a concept name and instructed to describe as many of the concept's descriptive features as they possibly can (McRae, Cree, Seidenberg, & McNorgan, 2005). These features include a concept's perceptual attributes (e.g., "is round" for apples), as well as its more propositional properties (e.g., "eaten in pies"). After collecting feature lists associated with each concept, researchers can code the responses as a binary vector, indicating whether each potential feature is associated with the concept. Then, the semantic similarity of individual objects can be compared to one another by calculating the proximity between their respective feature vectors, much in the same way that multi-voxel activity patterns are compared in neural similarity analyses.

Whereas studies that applied models of explicit, item-level judgments observed effects in pVTC and LOC, empirical work using models based on item-level feature vectors has found effects in perirhinal cortex. Clarke and Tyler (2014) scanned participants while they performed a basic-level naming task (e.g., "apple") for pictures of 131 different objects from a variety of categories. The similarity model was created from semantic feature norms, defined by lists of features associated with each concept. This analysis yielded an average of 13 descriptive features per concept, which included both visual and nonvisual properties.

Because variations in semantic features could be correlated with low-level visual properties and with taxonomic category membership, the authors also computed similarity structures generated according to these two additional spaces. In a whole-brain searchlight analysis, the authors used a partial correlation analysis to fit all three models at the same time. With this approach, they could examine the unique contribution of each model in predicting the neural similarity structure.

In agreement with prior findings, Clarke and Tyler (2014) found that category-based representations are most prominent in the posterior ventral stream, and that patterns in early visual areas matched the models of lower-level visual features. However, unlike previous work, the authors also detected more fine-grained similarity patterns in regions anterior to LOC. The object-specific model based on semantic features predicted the neural similarity space observed bilaterally in anterior medial temporal lobe and perirhinal cortex. Critically, these findings remained significant, even after controlling for neural similarity that tracked the category-level model and low-level visual feature model. Taken together, the results indicate that there are coarse, categorical representations most prominently in the posterior ventral stream, and more fine-grained similarity patterns in the anterior medial temporal lobe, which predict object-specific semantic similarity above and beyond that which is explained by models of categorical or visual similarity.

As reviewed earlier, prior studies have found that activation patterns in the posterior ventral stream correlate with human ratings of pairwise similarity (e.g., Connolly et al., 2012; Weber et al., 2009). In Clarke and Tyler's (2014) study, semantic feature effects were initially found in posterior VTC, but these effects became nonsignificant once the authors accounted for the variance in the neural data explained by the models of categorical and visual similarity. This finding leads to a couple of ways to interpret object-specific effects that have previously been reported in VTC. One is that within-category effects that have been previously reported in posterior VTC are driven by visual similarity.

Alternatively, it is possible that VTC activity encodes conceptual information that is not well captured by the object-specific model employed by Clarke and Tyler (2014). Although participant-produced feature lists have some advantages over explicit similarity judgments, there are also some drawbacks to this metric of similarity. Feature norming data tend to underrepresent information that is obvious or highly shared among the sampled concepts (e.g., "breathes"; "is solid"). Moreover, the produced features are limited to those that participants can easily verbalize. It will be a challenge for future work to examine the correspondence between semantic similarity models constructed from feature vectors and explicit pairwise ratings, and whether any divergences between these models can further characterize how object concepts are represented in the ventral stream.

Do Similarity Spaces Encode Modality-Independent Semantic Information?

Thus far, we have reviewed studies that examine the neural similarity spaces evoked by pictures of real-world objects. As noted earlier, the use of visual stimuli makes it difficult to distinguish between the contributions of perceptual versus semantic properties on an observed pattern of activity. One strategy for avoiding stimulus-driven perceptual effects is to measure multi-voxel patterns that are evoked when concepts are presented as words, because the semantic similarity and orthographic similarity are orthogonal stimulus dimensions.

In addition to using word stimuli, neuroscientists are interested in the similarities and differences in multi-voxel patterns evoked by a concept when it is accessed using different stimulus modalities (e.g., in picture or word form). In order to understand the meaning of a concept denoted by a word or a picture, we must retrieve the underlying representation, and meaning is evoked regardless of the format in which the concept is retrieved. For example, reading the word *hairbrush* should lead to the retrieval of conceptual content that is generally similar to the representation that is activated when one identifies a picture of a hairbrush. Brain areas that are involved in semantic retrieval are interpreted as representing high-level object representations that can be accessed from different stimulus modalities.

To what extent is meaning encoded in modality-independent systems? In attempts to further target neural representations of conceptual information, researchers have investigated the extent to which the multi-voxel patterns evoked by object concepts are invariant to the stimulus format with which the representations are accessed. These studies have implicated a number of regions, but researchers are still actively investigating the extent to which these putatively modality-independent neural similarity spaces represent conceptual information.

Cross-Modal Category Decoding

One way to identify regions that encode semantic information across different stimulus modalities is to use MVPA decoding methods. In these experiments, researchers test whether a classification algorithm trained on neural data from one modality can accurately classify unseen neural data evoked by the stimuli when they are presented in a different modality (Kaplan, Man, & Greening, 2015). Several studies have accurately classified stimulus classes across two stimulus modalities (e.g., words and pictures of tools versus dwellings in Shinkareva, Malave, Mason, Mitchell, & Just, 2011; spoken and written words of animals versus tools in Akama, Murphy, Na, Shimizu, & Poesio, 2012), and, in bilingual subjects, from concepts accessed in one language to another (e.g., Buchweitz, Shinkareva, Mason, Mitchell, & Just, 2012; Coreira et al., 2014). The brain areas that are identified by this line of research are interpreted as carrying information about the stimulus content, abstracted from the format in which the information is presented.

In one application of this approach, researchers were able to classify objects according to their semantic category across four different stimulus modalities. Subjects performed a semantic categorization task on various animals and tools. These stimuli were separately presented as photographs, written names, spoken names, and natural sounds (Simanova, Hagoort, Oostenveld, & van Gerven (2012). The authors used a classifier algorithm to discriminate between the animals and tools by iteratively training the classifier based on data from three of the modalities, and then testing the classifier's decoding accuracy on the fourth, excluded modality. The authors found that large portions of left VTC, bilateral frontal gyrus, and posterior middle temporal gyrus (pMTG) exhibited cross-modal classification of category membership. These results suggest that the neural activity patterns evoked by animals versus tools are discriminable, regardless of whether the stimulus objects are presented auditorily, visually, or verbally. The authors suggest that these regions support semantic knowledge representation by integrating information that originates from different input streams, and abstracting from low-level perceptual features to higher-level conceptual processing.

Cross-Modal Similarity Spaces

To what extent do regions implicated in modality-independent processing contribute to the representation of conceptual content? Perhaps the brain regions that can decode object category across modalities perform distinctive mental operations for each category, but these cognitive processes might not reflect semantic information. Some researchers have suggested that in order for a region that exhibits cross-modal decoding to be interpreted as representing conceptual content, it should play a role in distinguishing among representations of different objects and object categories; that is, the activity patterns in such a region would correspond with a model of semantic similarity. To addition to broad classification tests, researchers have also examined neural similarity spaces within brain regions that exhibit cross-modal decoding.

Between-Category Cross-Modal Findings

To further gain traction on whether the neural activity in putatively modality-independent brain regions reflects semantic information, Fairhall and Caramazza (2013) conducted an MVPA study using word and picture stimuli of objects from five semantic categories (fruits, clothes, tools, mammals, and birds). These authors proposed that if a region exhibits cross-modal decoding, in order to represent conceptual content, that region should support distinctions between different object categories. The authors tested this prediction by searching for modality-independent brain regions whose neural similarity structures matched category-defined semantic similarity structures.

During scanning, subjects made category typicality judgments in response to individual exemplars from five different categories (e.g., how typical is an apple of the category *fruit*?). The stimuli were presented as words in the first half of the experiment and then as pictures in the second half, so that word presentations were not confounded by prior exposure to particular images. The authors then trained a classifier to decode the distinct neural activity associated with each of the five semantic categories, independently of the process through which these representations were accessed (i.e., the stimulus modality). The classifier was then trained on the category-evoked patterns from each modality for subsequent testing on the data from the other modality (e.g., train on picture data; test on word data, and vice versa). Hence, only the category-specific information that was general to both modalities was informative to the classifier.

In regions that exhibited cross-modal category decoding, the authors related the observed category-level neural similarity space to the predicted model of category-based similarity structure. Rather than predicting a binary model of category membership, the authors quantified continuous gradations of similarity between each category pair. Such a model quantifies the similarity space at the category level, where, for example, birds are more similar to mammals than they are to fruits.

The cross-modal MVPA searchlight classifications revealed a network of six left-lateralized regions, mostly outside of category-selective visual cortex, in which there was overall cross-modal sensitivity to semantic category. The cross-modal decoding was identified in VTC, which included fusiform gyrus, parahippocampal gyri, and perirhinal cortex; pMTG; angular gyrus (AG); posterior cingulate and precuneus; and lateral and dorsomedial prefrontal cortex. Additionally, cross-modal neural similarity spaces in left VTC and left pMTG predicted semantic relationships among the object categories. This correspondence supports the view that these regions encode modality-independent conceptual information.

The identification of six regions that are sensitive to semantic category information across modalities—but only two of which are sensitive to the semantic similarities among categories—potentially indicates a functional dissociation between areas that represent category-based semantic similarities, and areas that are engaged in conceptual processing regardless of stimulus modality, but are not necessarily involved in representing conceptual content. More specifically, a brain region implicated in modality-independent conceptual processing might play a role in operating upon or accessing semantic representations, without necessarily representing the content itself. These potential distinctions between cognitive operations and cognitive content are entirely speculative; we will return to the issue of interpreting whether multi-voxel patterns reflect semantic processing versus semantic representations in a later section.

Comparing Word and Picture Similarity Spaces

These studies demonstrate that classifier-based decoding methods can identify regions involved in cross-modal semantic processing by training on data from one modality and testing against data from the other modality. Additionally, the findings in Fairhall and Caramazza (2013) suggest that some of these regions are also sensitive to category-level similarities between objects. But do modality-independent regions represent the same similarity relations among semantic representations, regardless of whether they are accessed by word or picture format? A region might be involved in semantic processing for both words and pictures, but that region might engage in distinct, modality-specific networks for each modality. In such a case, the underlying neural similarity spaces might differ across modality, even if the region encodes semantic content from each of the modalities.

To determine the computational commonalities and differences for accessing concepts in picture or word format, Devereux and colleagues (2013) compared neural similarity spaces evoked by concepts first presented as words and then as pictures. The multi-voxel patterns were computed from brain activity while subjects named the category of the presented stimulus object (e.g., “clothes” for a sweater). The objects included

10 different exemplars from six common semantic categories (e.g., insects; vegetables). A category-level similarity model was constructed, such that stimulus pairs from the same category were predicted to evoke more similar patterns than pairs from different categories (as in Figure 22.2).

The neural similarity structures yielded by the word data and the picture data were then compared to one another. This analysis tests whether the pairwise neural similarities observed in response to the word stimuli match the neural similarity space observed from the picture stimuli. Further, to determine the extent to which these neural similarity spaces reflected semantic content, the word-based and picture-based neural similarity spaces were each compared to the model of category-level representation. The category-level model matched the picture-evoked data in VTC, and the word-evoked data in anterior MTG. Additionally, several regions exhibited neural-semantic correspondence for each separate stimulus modality, including the MTG, AG, and left inferior parietal sulcus (IPS).

To explore the similarities between the neural similarity spaces across modalities, the neural similarity spaces from the two modalities were compared in a data-driven clustering analysis, such that similar spaces would cluster together. This method can identify representational invariance both across modalities, and also across brain regions, because the clustering algorithm is blind to whether similar searchlights spatially correspond to one another. In contrast, cross-modal classifier methods, like those used by Simanova et al. (2012) and Fairhall and Caramazza (2013), presuppose that common representational content is only found in the same set of corresponding voxels across modalities.

This analysis revealed that left IPS was relatively invariant to stimulus modality, as its word and picture neural similarity spaces clustered together. The representational invariance observed here suggests that the semantic feature information required to perform the category-naming task does not differ as a function of stimulus modality in this region. Additionally, though word-based and picture-based neural similarity structures in left MTG each separately correlated with the semantic model, they did not cluster together. These findings suggest that the left MTG performs modality-specific functional roles that yield distinct yet overlapping neural responses. Such a finding has important consequences for research investigating modality-invariant semantics, because it demonstrates that identifying regions involved in both word and picture processing—and even discovering that they both correspond to a common semantic similarity model—is insufficient to claim that they form part of a common modality-independent semantic network.

The analyses in Devereux, Clarke, Marouchos, and Tyler. (2013) go beyond identifying individual regions involved in modality-independent, category-sensitive processing, and illustrate how the response properties of a region can vary as a function of the modality-specific network in which it is engaged. Whereas findings in Fairhall and Caramazza (2013) indicated that MTG encodes semantic content in both modalities, Devereux and colleagues (2013) revealed that each modality evokes a distinct neural similarity space in MTG. These advanced approaches are uniquely enabled by the comparison of neural similarity spaces evoked by multi-voxel patterns, independent of the modality in which they are sampled.

Within-Category Cross-Modal Findings

In contrast to reports of category-level distinctions and similarities across modalities, Bruffaerts et al. (2013) and Liuzzi et al. (2015) limited their investigation of cross-modal neural similarity spaces to concepts from a single superordinate category: animals. Although these two studies employed the same stimuli and experimental task, they probed neural responses using two different stimulus modalities: Bruffaerts et al. (2013) visually presented the animal stimuli as words and pictures, and Liuzzi et al. (2015) presented them as written words (i.e., visual presentation) and spoken words (i.e., auditory presentation). In both cases, semantic clusters and concept similarities were determined in a data-driven manner, on the basis of a concept-feature data matrix derived from a behavioral study, similar to the feature-norming data used by Clarke and Tyler (2014). During scanning, subjects performed a property verification task on the stimuli (e.g., "has wings?").

Bruffaerts et al. (2013) and Liuzzi et al. (2015) tested whether the average neural similarity in response to stimuli from the same within-category semantic cluster was greater than would be expected by chance. The analysis was performed regardless of stimulus modality, and then again in each modality separately. Bruffaerts et al. (2013) found that the left perirhinal cortex and left anteromedial fusiform gyrus exhibited above-chance within-cluster similarity. They observed this pattern of results when word and picture responses were pooled together; however, a follow-up analysis revealed that the neural responses evoked by the word stimuli were driving these effects. Liuzzi et al. (2015) replicated this correspondence between the neural and semantic similarity spaces in the same area of left anteromedial fusiform gyrus. However, as in Bruffaerts et al. (2013), this effect was limited to visually presented words. Moreover, Liuzzi et al. (2015) also observed effects for written words in left perirhinal cortex: this region exhibited greater neural similarity for stimuli from the same versus a different semantic cluster.

The results from Bruffaerts et al. (2013) and Liuzzi et al. (2015) indicate that, in response to visually presented words, semantic similarity is reflected at a fine-grained level in regions of left perirhinal cortex. This finding comports with Clark and Tyler's (2014) observed correlations between fine-grained measures of feature similarity and object-specific responses to pictures in bilateral perirhinal cortex. Additionally, this region partly overlaps with the ventral temporal region that exhibited cross-modal category selectivity in Fairhall and Caramazza (2013).

It is unclear why responses in left perirhinal cortex exhibited cross-modal effects in Fairhall and Caramazza (2013), but not in Bruffaerts et al. (2013) or Liuzzi et al. (2015). One possible explanation for null result in response to spoken-word presentations is that the perirhinal cortex is specialized for visual input. Additionally, the authors suggest that the degree to which perirhinal cortex reflects cross-modality semantic similarity might vary as a function of task demands. For instance, perhaps subjects performed some of the property verification tasks (e.g., "smooth?"; "exotic?") on picture stimuli in Bruffaerts et al. (2013) by relying upon the depicted perceptual features, and without accessing semantic information. This raises the possibility that neural similarity spaces are dynamically influenced by task- and stimulus-based factors. We discuss this topic in the next section.

HOW ARE SIMILARITY SPACES ALTERED BY EXPERIENCE?

Thus far, we have reviewed studies that examined correspondences between neural and semantic similarity spaces. These studies also have explored how the neural similarity structures vary across brain regions and across stimulus modalities. In addition to these broad research questions, some studies have investigated how neural similarity spaces might vary across tasks or individual experience. This line of research reveals that neural activity evoked by objects—and consequently, the observed neural similarity space—can flexibly adapt in response to changes in experimental task or context.

Manipulating Object Category

One potential way to alter a similarity space is to manipulate the salience of the dimensions that distinguish between object categories. One might predict that if category members are modified such that they receive more similar responses to one another and more distinct responses relative to non-members, then these changes might be evident in the resulting similarity space. A study by Dunsmoor and colleagues (2013) tested how one such category-level manipulation might affect a neural similarity space.

These authors investigated how category-level neural similarity structures can be modulated by aversive fear learning. In this study, fMRI subjects viewed images from two object categories: animals and tools. During the scanning session, basic-level exemplars were presented one at a time while subjects rated their expectancy of receiving a shock. Unbeknownst to the subjects, one group of subjects learned through experience that presentations of animal stimuli were sporadically associated with an aversive electrical shock and that images of tools were safe, and a separate group learned the opposite contingencies. The authors predicted that multi-voxel patterns of activity in object-selective cortex would exhibit enhanced representational similarity among different category members from the feared category. Such a mechanism might facilitate the transfer of affective learning between semantically related objects.

For this analysis, the authors examined patterns of neural activity within object-selective regions of bilateral occipitotemporal cortex. The authors compared the average pairwise neural similarity within and between object categories, to determine whether the within-category neural similarity for the shocked category was different from the within-category neural similarity for objects from the safe category. This analysis revealed that in both subject groups, activity patterns in object-selective cortex were more similar among exemplars from the threat versus safe category.

These results suggest that aversive learning selectively enhances representational similarity among categorically related exemplars. The representational structure of these categories was functionally altered in an experience-dependent fashion, as aversive learning selectively enhanced the neural similarity space of the object category that acquired threat value. The authors hypothesize that this effect might support within-category generalization, such than an emotional experience with one instance of an object category leads to generalizations about the properties of related objects through induction (Murphy, 2002).

Manipulating Object Features

Rather than modifying the salience or the distinctiveness of the response required for an entire object category, one could also modify the salience of a particular stimulus dimension by manipulating whether or not that dimension was necessary to perform a cognitive task. One might predict that if one stimulus dimension (e.g., object color) was made relevant for one group of subjects but not for another, then the first group's neural similarity space might reflect sensitivity to this dimension, while the second group's would not.

This prediction was tested in a paper by Hsu and colleagues (2014). To examine the impact of feature diagnosticity on concept representations, these authors taught participants a set of novel objects that were each labeled with a novel name. In a between-subjects design, the authors manipulated whether or not color knowledge was necessary for identifying each novel object. Half of the subjects learned that shape was sufficient to distinguish between objects in the stimulus set (the S subjects), while the other half learned that the conjunction of shape and color was diagnostic of object identity (CS subjects). After subjects were trained to learn the object names, subjects' neural activity was measured while they performed a shape memory task on these objects.

The authors hypothesized that the retrieval of diagnostic feature information would yield group-level differences in the extent to which pairwise similarity ratings of these objects would predict the neural similarity space constructed from neural activity measured during the shape knowledge task. Specifically, the authors predicted that (1) general similarity ratings and (2) ratings based on color similarity of the stimuli would predict the neural similarity space observed in the CS subjects, but not in the S subjects. Moreover, this effect should emerge in color-sensitive brain regions.

For this analysis, a color-sensitive region of left fusiform gyrus was used as an fROI. The authors extracted the multi-voxel patterns evoked in response to shape retrieval associated with each object and computed the resulting similarity space. They then assessed whether this neural similarity space could be predicted by three sets of behavioral similarity ratings: one previously obtained from the trained subjects in response to the object names, and two obtained from untrained subjects, who rated the object pictures based on their color similarity.

The results indicated that the color similarity ratings approached significance for predicting the neural similarity space in the CS subjects, but not for the S subjects. Further, the between-group correlations were reliably different from one another. Because color did not provide the same diagnostic information for S subjects as it did for the CS group, this may explain the lack of correlation between color-based similarity and neural similarity for the S group. These findings demonstrate that the use of feature knowledge affects conceptual representations, and that the learned context of an object can influence its conceptual representation.

Manipulating Object Familiarity

To explore how object representations in VTC differ across individuals, Charest et al. (Charest, Kievit, Schmitz, Deca, & Kriegeskorte, 2014) measured neural activity patterns while subjects viewed two separate stimulus sets: one composed of pictures of faces, places, bodies, and objects that were personally meaningful to the subject (e.g., a friend's face, his or her own backpack), and one set composed of pictures that were unfamiliar to the subject (e.g., pictures that were personally meaningful for another, unknown subject). For each separate stimulus set, subjects also judged the relative similarities among the pictures. The authors found that the neural similarities in VTC more closely matched each subject's own similarity judgments (relative to other subjects' judgments) when the stimulus set was personally meaningful. Such a result suggests that the neural similarity spaces in VTC reflect our unique, subjective perception of real-world objects and their similarity relationships. Moreover, this finding illustrates that subtle individual differences in neural representations of objects can be uncovered with similarity-based approaches.

WHAT DO MULTI-VOXEL PATTERNS MEASURE?

Theoretical Challenges

As with any method, the results yielded by similarity-based analyses must be interpreted with some caution. Here, we review some of the challenges in making sense of the information reflected in the similarity between neural activity patterns elicited by thoughts about concepts.

The dominant theory behind these investigations is that representations of concepts can be conceived of as points in a high dimensional space. Testing hypotheses about the content and structure of neural representational spaces requires measuring the relationships between neural signals evoked by thoughts about various concepts. This approach strongly depends on the assumption that the multi-voxel patterns evoked by thinking about a concept constitute the neural representation of that concept. This assumption is most notably evident in the term that Kriegeskorte and colleagues (2008) coined to describe similarity-based analyses of multi-voxel patterns: "Representational Similarity Analysis," or RSA. This term helpfully provides a common name for studies to invoke when they introduce their methodological approach. However, it is important to point out that the "R" in RSA comes with a caveat.

The use of the term "representation" suggests a detectable and meaningful distinction between representations, which are codes that store informational content, and processes, which are mechanisms that create and operate upon these representations (cf. Davis & Poldrack, 2013). These terms are often rhetorically useful for developing and testing hypotheses about various cognitive mechanisms and underlying representational structures. However, the distinction between the two is often uninterpretable, because fMRI can only measure representations while they are in use, that is, while they are being operated upon by some process. Hence, the multi-voxel patterns evoked by a given representation are inseparable from the set of processes that are currently operating upon that representation. For the purposes of characterizing human cognition, the distinction between process and representation might be inconsequential, because a thought must be accessed in order to be known. It is a matter of philosophical debate whether inaccessible thoughts contain meaningful content, and whether they even exist.

But, the lack of a distinction between process and representation potentially qualifies the results yielded by neural similarity analyses. These analyses are incapable of targeting the multi-voxel patterns that are exclusively evoked by conceptual representations. In fact, so-called RSA methods are just as sensitive to process-level differences between stimuli as they are to representation-level differences. As a consequence, any observed relationships between the multi-voxel patterns evoked by two stimuli might occur because the stimuli are representationally similar, but they might also occur because the two stimuli both require the engagement of a common cognitive process.

Methodological Challenges

While it is impossible to fully dissociate process-level and representational accounts, researchers can design their studies such that the confounds between processes and representations are minimized. For instance, to reduce the impact of processes on multi-voxel patterns, the patterns could be sampled while subjects perform a secondary task that is orthogonal to the representational aspects of the stimuli that are being studied. Additionally, basic processes like familiarity and complexity should be uncorrelated with the dimensions of the representational space. In a thoughtful commentary, Davis and Poldrack (2013) propose additional experimental solutions to this issue.

These suggestions highlight the fact that multi-voxel patterns will likely reflect a number of nonrepresentational signals that overlap with the stimulus-evoked responses. These signals might reflect the engagement of a cognitive process, or other characteristics that differ between stimulus conditions, including differences in the signal-to-noise ratio between conditions, perhaps due to differences in memorial and attentional resources that have been allocated to one condition versus the other (cf. Todd, Nystrom, Cohen, 2013). These spurious sources of reliability in multi-voxel patterns could underlie any observed differences in similarities between conditions. Likewise, any potential downstream effects, such as differences between conditions in task difficulty or response latencies, could contribute to the similarity of the observed neural patterns.

Future Directions and Summary

A growing number of studies have explored modality-specific and cross-modal conceptual representations of objects by highlighting the commonalities between the neural similarity structures evoked with and between object categories. One potential avenue for future research is to further characterize the semantic similarity spaces that best predict modality-specific effects. Moreover, additional studies could explore how stimulus modality, experimental task, and object-specific properties can each uniquely and jointly shape the resulting neural similarity space.

Future investigations might benefit from constructing similarity spaces that are defined by object relatedness according to specific dimensions (e.g., shape or color similarity). With this approach, researchers can investigate the specific semantic features that best predict the observed neural similarity spaces. The studies reviewed here have quantified conceptual similarity at a far more general level: according to objects' taxonomic category (as in Devereux et al., 2013; Fairhall & Caramazza, 2013; Haxby et al., 2001); superordinate, within-category object class (e.g., Bruffaerts et al., 2013; Connolly et al., 2012); or basic-level, within-category comparisons that are either based on pairwise ratings of overall relatedness (e.g., Connolly et al., 2012; Weber et al., 2009); or comparisons between object vectors that code over a dozen object features (e.g., Bruffaerts et al., 2013; Clarke & Tyler, 2014)

These studies indicate that semantically related concepts evoke similar representations. But given how these studies measure similarity, they cannot fully characterize the features (or feature combinations) that are responsible for the correspondence between the neural and semantic similarity spaces. What information is driving the observed neural representational structures? Using data-driven analyses, researchers can more closely explore and observe neural similarity spaces and attempt to extract their most informative dimensions. And in hypothesis-driven analyses, one can systematically vary the dimensions that are predicted by a semantic model of the similarity space.

In sum, this line of research illustrates a progression in the types of questions that researchers have asked, based on the complexity and sensitivity of the analysis techniques that have become available. Traditional univariate-based analyses identified regions that were "commonly activated" by pictures and words; MVPA decoding methods identified regions where neural patterns could discriminate between broad object classes across stimulus modalities; and similarity-based methods have since identified whether these putatively modality-independent regions are sensitive to more fine-grained similarities among concepts. The advent of MVPA techniques has brought about a shift in how analyses of conceptual content are both conducted and interpreted in the brain. These methods provide increased sensitivity for detecting the representational structure that underlies concept-specific and even feature-specific representations. Given this unique sensitivity and flexibility, neural similarity analyses are an essential part of the neuroscientist's toolkit.

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CHAPTER 23

THE HOW AND WHAT OF OBJECT KNOWLEDGE IN THE HUMAN BRAIN

FRANK E. GARCEA AND BRADFORD Z. MAHON

INTRODUCTION

THE ability to manipulate objects in order to carry out complex tasks is a fundamental cognitive ability that we utilize on a daily basis: we are constantly recognizing, grasping, and manipulating objects (e.g., pliers, scissors, fork, etc.). Despite the indefinite number of ways in which one could, in principle, interact with objects in the environment (Wu, 2008), we grasp and manipulate objects in a specific manner: in order to carry out their function and satisfy behavioral intentions. Thus, everyday tool use requires the integration of action knowledge in the motor domain (i.e., knowing how to physically manipulate a pair of scissors) with abstract conceptual knowledge (i.e., knowing the function of scissors) in order to manipulate an object according to the goal or purpose of use (cutting a piece of paper). The objective of this chapter is to review the main elements that must be satisfied by a cognitive model of tool processing, including object recognition and object use, and to situate that model in the context of what we currently know about the neural substrate of tool processing.

SCOPE OF THE CHAPTER

The goal of this review is to argue for two empirical hypotheses: (1) function and manipulation knowledge are dissociable types of information about manipulable objects; and (2) there are specific neural pathways and regions involved in integrating knowledge of object function and object manipulation during tool use. We review three principal sources of evidence: (1) functional neuroimaging studies measuring blood oxygenation level dependent (BOLD; see Heim & Specht, Chapter 4 in this volume) signal when healthy adults retrieve knowledge of object function and object manipulation; (2) cognitive dissociations between object function and object manipulation in neuropsychological patients; and (3) transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume) studies measuring the online retrieval of function and manipulation knowledge.

More broadly, and to situate our review of tool processing alongside the other contributions that form this volume, there are interesting parallels to be explored between function and manipulation knowledge, on the one hand, and between lexical-semantic and lexical knowledge, on the other hand. In their seminal theoretical review, Rothi, Ochipa, and Heilman (1991) distinguished between what they referred to as 'action semantics' and the 'Action output lexicon' (for discussion and development, see also Cubelli et al., 2000; Negri, Rumiati, et al., 2007). The distinction between semantic information pertaining to objects and actions, and high-level descriptions of object-directed actions, is important and warrants further close scrutiny. As will be described in the following, a defining feature of "upper limb apraxia" is a deficit in the skilled use of the hands that cannot be explained by elemental motor deficits; this may be akin to patients with anomia, who do not have difficulty with articulation of words, or with accessing word meaning, but rather with interfacing meaning with articulation. As Rothi and colleagues, and a number of others, have emphasized, patients with apraxia can retain the ability to imitate actions, much like patients with anomia can retain the ability to repeat words (e.g., see Tessari, Canessa, Ukmar, & Rumiati, 2007). We return later to consider these potentially fruitful parallels between the praxis and the language systems.

OVERVIEW OF TOOL PROCESSING IN THE HUMAN BRAIN: THE TOOL-PROCESSING NETWORK

The Dorsal and Ventral Visual Pathways

An influential model of visual processing, motivated in large part by the work of Melvyn Goodale and David Milner, distinguishes between a ventral visual pathway and a dorsal visual pathway (e.g., see Goodale, Milner, Jakobson, & Carey, 1991; Goodale & Milner, 1992; see also Livingstone & Hubel, 1988; Merigan & Maunsell, 1993; Ungerleider & Mishkin, 1982). The dorsal/ventral stream hypothesis argued that visual information is processed by separate anatomical and functional pathways in the visual system: The ventral visual pathway, which courses ventrally from primary visual cortex to inferotemporal cortex, processes visual input in the service of object identification and long-term memory retrieval and encoding; the dorsal visual pathway, which projects subcortically and cortically, potentially via motion sensitive area MT/V5 as well as striate cortex, to dorsal occipital and posterior parietal cortex (e.g., Almeida, Mahon, Nakayama, & Caramazza, 2008; Culham et al., 2003; Fang & He, 2005; Gallivan, McLean, Flanagan, & Culham, 2013; Kristensen, Garcea, Mahon, & Almeida, 2016; Lyon, Nassi, & Callaway, 2010; Mahon, Kumar, & Almeida, 2013; Sincich, Park, Wohlgemuth, & Horton, 2004), processes volumetric information about objects in egocentric frames of reference in the service of online object-directed actions (for reviews, see Binkofski & Buxbaum, 2013; Milner & Goodale, 2008; Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006; Rossetti, Pisella, & Vighetto, 2003; see also de Haan & Cowey, 2011).

The Tool-Processing Network

During the same period in which the dorsal/ventral stream hypothesis was coming into focus, Alex Martin and colleagues carried out a series of functional MRI experiments on semantic category representation that permanently changed the theoretical landscape. In their early reports, Chao, Martin, and colleagues reported that viewing pictures of tools compared to baseline categories (e.g., faces, vehicles, animals) elicited differential BOLD contrast in the medial fusiform gyrus bilaterally and the left posterior middle temporal gyrus (e.g., see Chao, Haxby, & Martin, 1999), as well as in the inferior and superior parietal lobule, dorsal occipital cortex, and premotor cortex (e.g., see Chao & Martin, 2000; see also Almeida, Fintzi, & Mahon, 2013; Culham, Danckert, DeSouza, Gati, et al., 2003; Fang & He, 2005; Garcea & Mahon, 2014; Mahon, Kumar, & Almeida, 2013; Mahon, Milleville, Negri, Rumiati, Caramazza, & Martin, 2007; Noppeney, Price, Penny, & Friston, 2006; Peeters, Rizzolatti, & Orban, 2013; Rumiati, Weiss, Shallice, Ottoboni, Noth, et al., 2004; for reviews, see Lewis, 2006; Martin, 2007, 2009, 2016). Differential BOLD contrast for tools is generally left-lateralized, with the exception of the medial fusiform gyrus, and superior/posterior parietal cortices. Collectively, we refer to this entire brain network of regions as the "tool-processing network" (see Figure 23.1).

Different regions within the network of regions shown in Figure 23.1 support different aspects of tool processing. Regions within ventral temporal-occipital cortex process visual features such as surface texture (e.g., see Cant & Goodale, 2007, 2011), color (e.g., see Miceli, Fouch, Capasso, Shelton, Tomaiuolo, & Caramazza, 2001; Stasenko, Garcea, Dombovy, & Mahon, 2014), and object weight (e.g., see Gallivan, Cant, Goodale, & Flanagan, 2014). Functional MRI studies have found that patterns of unarticulated motion associated with tools in use are represented in the left posterior middle temporal gyrus (e.g., see Beauchamp, Lee, Haxby, & Martin, 2002, 2003). Additional neuropsychological investigations have reported an association between lesions in the vicinity of the left posterior middle temporal gyrus and impairments in tool recognition (e.g., see Brambati et al., 2006; Campanella, D'Agostini, Skrap, & Shallice, 2010; Mahon et al.,

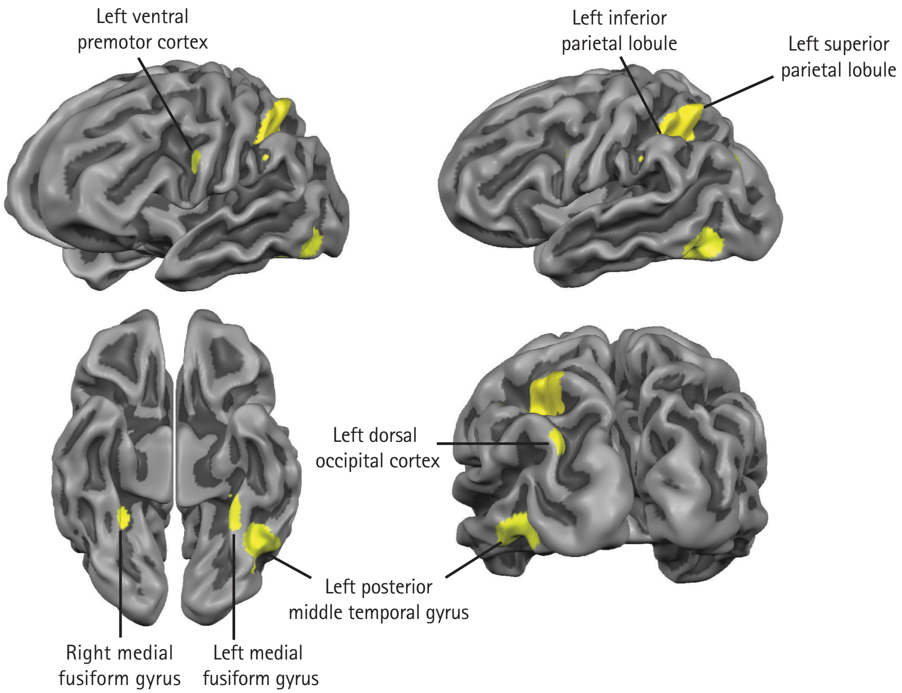

Left ventral premotor cortex
Left inferior parietal lobule
Left superior parietal lobule
Left dorsal occipital cortex
Left posterior middle temporal gyrus
Right medial fusiform gyrus
Left medial fusiform gyrus

FIGURE 23.1. Cortical regions in the dorsal stream, the ventral stream, and frontal-motor cortex that comprise the tool-processing network. Undergraduate participants viewed images of tools and animals (among other stimuli). These data replicate a pattern originally reported by Chao and colleagues (1999) and Chao and Martin (2000). Plotted in yellow are the regions of cortex that express increased BOLD contrast for images of manipulable objects (contrast: tools > animals). Specifically, viewing images of manipulable objects elicits increased BOLD contrast in dorsal and ventral premotor cortex, left parietal cortex in the vicinity of the anterior intraparietal sulcus, the left posterior middle/inferior temporal gyrus, bilateral posterior parietal/dorsal occipital cortex, and medial fusiform gyrus bilaterally (for details, see Garcea and Mahon, 2014; Chen et al., 2016; Chen et al., 2018).

2007; Tranel, Damasio, & Damasio, 1997), and in the retrieval of conceptual knowledge associated with actions (e.g., see Buxbaum, Shapiro, & Coslett, 2014; Tranel, Kemmerer, Adolphs, Damasio, & Damasio, 2003). The left ventral premotor cortex (e.g., see Chao & Martin, 2000) and left dorsal premotor cortex (e.g., see Grafton, Fadiga, & Rizzolatti, 1997) have been argued to support the planning and sequencing of complex actions. The left dorsal occipital cortex, in the vicinity of left posterior parietal cortex, is hypothesized to process volumetric and spatial information, likely in body-centered coordinates, necessary for accurate reaching and grasping. Lesions to posterior parietal and/or dorsal occipital cortex are associated with optic ataxia, a visuomotor impairment for reaching and/or grasping in peripersonal space (Desmurget & Sirigu, 2009; Jeannerod, Arbib, Rizzolatti, & Sakata, 1995; Jeannerod, Decety, & Michel, 1994; Karnath & Perenin, 2005; Pisella, Gréa, Tilikete, & Vighetto, 2000).

In order to use objects to satisfy behavioral goals, it is necessary to access stored information about how to manipulate the object according to its function—for instance, to use a hammer to pound a nail, the hammer must be gripped off of its center of mass, and swung in a particular manner, ensuring that a particular aspect of the head of the hammer makes contact with the nail. A long tradition of neuropsychological research has described a level of action representation that corresponds to the "knowledge" of how to manipulate an object according to its function—we term this *manipulation knowledge*. Patients with limb apraxia have impairments when performing skilled actions, which manifests as an impairment in using objects according to their function. Limb apraxia is associated with lesions to the left inferior parietal lobule, in the vicinity of the supramarginal gyrus (e.g., see Liepmann, 1905; see also Bartolo, Cubelli, Della Sala, Drei, & Marchetti, 2001; Buxbaum, Veramonti, & Schwartz, 2000; Halsband, Schmitt, Weyers, Binkofski, Grutzner, & Freund, 2001; Mahon et al., 2007; Negri, Rumiati, Zadini, Ukmar, Mahon, & Caramazza, 2007; Garcea, Dombovy, & Mahon, 2013; Ochipa, Rothi, & Heilman, 1989; Rapcsak, Ochipa, Anderson, & Poizner, 1995; Rumiati, Zanini, Vorano, & Shallice, 2001; for reviews, see Binkofski & Buxbaum, 2013; Buxbaum, 2017; Cubelli, Marchetti, Boscolo, & Della Sala, 2000; Goldenberg, 2009; Johnson-Frey, 2004; Mahon & Caramazza, 2005; Osiurak & Badets, 2016; Rothi, Ochipa, & Heilman, 1991). Functional neuroimaging studies converge with the view that the left inferior parietal lobule represents complex manipulation knowledge, as there is increased BOLD contrast in the left inferior parietal lobule when healthy adults view images of manipulable objects (e.g., Almeida et al., 2013; Chao & Martin, 2000; Garcea, Kristensen, Almeida, & Mahon, 2016; Kristensen, Garcea, Mahon, & Almeida, 2016; Garcea & Mahon, 2014; Mahon et al., 2007; Mahon et al., 2013; for reviews, see Lewis, 2006; Martin, 2007) or pantomime object use while in the scanner (Chen, Garcea, & Mahon 2016; Choi et al., 2001; Moll et al., 2000; Rumiati et al., 2004).

Neuroimaging work focusing on the reaching and grasping components of object use have dissociated subregions within the left superior parietal lobule where BOLD signal is maximal for reaching, while BOLD signal in regions of the left anterior intraparietal sulcus (aIPS) is maximal for grasping (e.g., see Cavina-Pratesi, Goodale, & Culham, 2007; Culham, Danckert, DeSouza, Gati, et al., 2003; Konen, Mruczek, Montoya, & Kastner, 2013; Rossit, McAdam, Mclean, Goodale, & Culham, 2013). These human imaging studies parallel neurophysiological studies in macaques (e.g., see Galletti, Fattori, Kutz, & Gamberini, 1999; Murata, Gallese, Luppino, Kaseda, & Sakata, 2000; Sakata, Taira, Mine, & Murata, 1992).

Dissociations Between Manipulation Knowledge and Function Knowledge: Evidence from Cognitive Neuropsychological Studies

Selective Impairment to Manipulation Knowledge

Cognitive neuropsychological evaluations of patients with limb apraxia have pointed to a distinction between conceptual knowledge of objects and the ability to manipulate objects correctly according to their function. For instance, Ochipa, Rothi, and Heilman (1989) reported the performance of an individual who was able to identify (17/20) and point to objects from verbal command (19/20) that she could not use (2/20; see Figure 23.2 B, left inset; see also Garcea et al., 2013; Negri, Rumiati, et al., 2007; Rapcsak et al., 1995). In a series of studies, Laurel Buxbaum and her colleagues established key aspects of what we now understand about how manipulation and function knowledge are organized in the brain. Buxbaum, Veramonti, and Schwartz (2000) asked two limb apraxic patients to carry out a series of action production and semantic judgment tasks with manipulable objects. Those patients' abilities to use objects, complete multistep actions (e.g., making a sandwich), and make manipulation-based declarative judgments were grossly impaired; however, their ability to make function judgments over those same items was relatively spared (see Figure 23.2 A; see also Buxbaum & Saffran, 2002). Together, these reports demonstrate that knowledge of the identity and function of objects is dissociable from the ability to manipulate the object correctly after brain injury (for review, see Mahon & Caramazza, 2005).

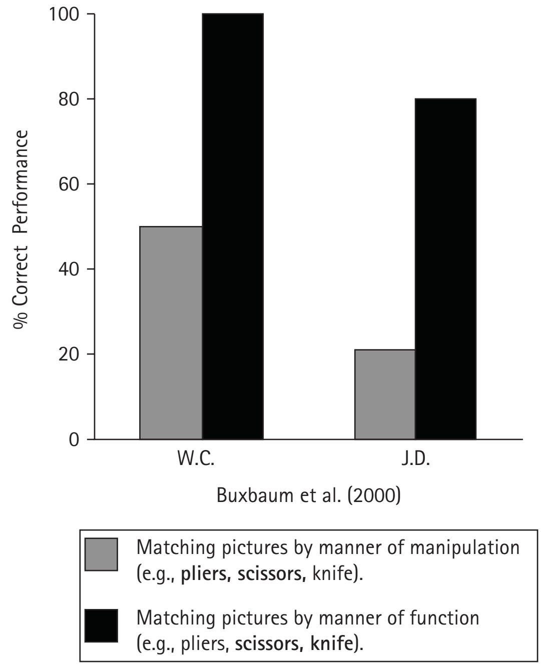
Additional evidence for that empirical generalization is provided by the findings of Rosci, Chiesa, Laiacona, and Capitani (2003). Those authors carried out a case series analysis with individuals who presented with and without limb apraxia after left brain damage; the participants were asked to point to pictures from verbal command, to imitate meaningful and meaningless gestures produced by the experimenter, to pantomime object use from the visual presentation of common manipulable objects, and to complete picture-word matching and picture-naming tasks. Rosci and colleagues reported that individuals with limb apraxia tended to have more severe naming deficits than those without apraxia, but at the single-case level, patients with severe apraxia remained able to name pictures and match pictures to their corresponding names (see also Negri, Rumiati, et al., 2007).

Somewhat tangentially, those neuropsychological dissociations between impaired use and spared general (including function) knowledge of objects has important implications for theories of the format of concept representation (for review and discussion, see Mahon & Caramazza, 2005, 2008; Mahon & Hickok, 2016). Specifically, the fact that high-level motor-relevant information about objects can be impaired while sparing other forms of semantic knowledge rules out strong forms of the so-called embodied cognition view, which argues that motor information is constitutively involved in the representation of semantic knowledge. We have further argued that weaker forms of the embodied view that drop the proposal that concepts are sensorimotor in their format do not fare better. Weakening embodied theories so that the core claim is no longer about the format of concept representation, but rather about conceptual content, renders the theory indistinguishable from the putative alternative theory, namely that concepts are represented as "abstract symbols" (for discussion, see Caramazza, Hillis, Rapp, & Romani, 1990; Mahon, 2015).

Selective Impairment to Function Knowledge

Several case studies and group-level analyses have demonstrated the opposite pattern of performance: following damage to the temporal lobes, patients can be impaired when

(a) The dissociation between function and manipulation knowledge.



(b). The double dissociation between object use and object naming.

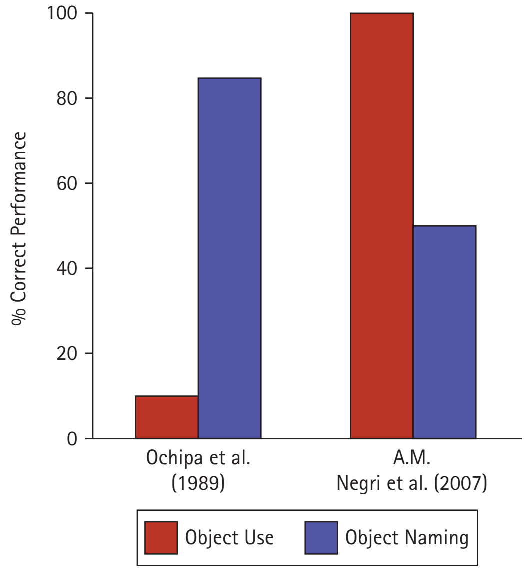


FIGURE 23.2. Neuropsychological dissociation between conceptual knowledge and praxis. (A) The dissociation between function and manipulation knowledge. Buxbaum, Veramonti, and Schwartz (2000) reported the performance of two individuals (W.C. and J.D.) in which object-associated manipulation knowledge was impaired relative to object-associated function knowledge. (B) The double dissociation between object use and object naming. Ochipa, Rothi, and Heilman (1989) reported the performance of an individual who was impaired with using objects in the face of spared object naming; in contrast, Negri, Lunardelli, and colleagues (2007) reported the performance of an individual (D.L.) who was within control range when using objects despite presenting with an impairment for naming objects, which worsened when tested two years later.

retrieving conceptual knowledge of objects that they can nonetheless successfully manipulate (e.g., see Negri, Lunardelli, Reverberi, Gigli, & Rumiati, 2007). While there are reports of patients with impairments to function knowledge due to viral infections affecting the anterior temporal lobes (e.g., see Sirigu, Duhamel, & Poncet, 1991), other investigations have been carried out with individuals with degenerative diseases like semantic dementia (SD), a disease that typically affects the anterior temporal lobes bilaterally, but asymmetrically (Negri, Lunardelli, et al., 2007). In the early stages of SD, individuals are typically impaired in expressive and receptive language, and in retrieval of conceptual knowledge of objects; as the disease progresses, their ability to retrieve conceptual knowledge of objects worsens, affecting their knowledge of people, common objects, and words. Despite these deficits, individuals with SD typically have spared visuospatial processing, intact phonological and syntactic processing, and intact executive control.

Because the effects of SD progress over time, researchers have focused on capturing the progression of SD and its longitudinal effect on conceptual processing and object-use abilities. Negri, Lunardelli, and colleagues (2007) performed a case-series analysis of two individuals, one with suspected SD, and another with Alzheimer's disease. Despite a gradual degradation of lexical-semantic knowledge of objects (especially tools) over a two-year period, Negri and colleagues showed that the two individuals were nonetheless able to successfully manipulate those objects, and that their object-use abilities, while also declining, did not decline as dramatically (see Figure 23.2 B, right inset). Those data present a puzzle: How are SD patients able to successfully manipulate an object when they have lost knowledge of what it is used for, or can no longer verbally describe its use? Hodges, Spatt, and Patterson (1999) addressed this question when they tested three participants; two of the participants had SD, while the third participant had been diagnosed with corticobasal degeneration (CBD); CBD is characterized by severe limb apraxic symptoms without ataxia or elemental sensory/motor dysfunction after damage to the basal ganglia, parietal lobes, and in some instances, frontal lobes. Hodges and colleagues showed that both SD participants were unable to name objects, and were at chance when judging the functions of objects. When contrasting the SD participants with the performance of the CBD participant, Hodges and colleagues reported that the CBD individual's naming performance and knowledge of object function, while marginally outside of control range, was markedly better. Interestingly, while the three participants were impaired when using objects, the SD participants were at ceiling when asked to carry out a novel tool-selection task, while the CBD participant was no different than chance. The novel tool-selection task probed mechanical problem-solving abilities by requiring participants to decide which of three novel tools would best fit into a socket. Taken together, Hodges and colleagues argued that SD participants were able to do well on the novel object-use task because mechanical problem-solving calls upon a system of reasoning that is independent of object knowledge (for recent discussion, see Buxbaum, 2017; Osiurak & Badets, 2016).

In a group-level analysis of SD participants, Hodges, Bozeat, Lambon Ralph, Patterson, and Spatt (2000) reported that SD participants were deficient when asked to use everyday objects, as well as retrieve conceptual/functional information about those same objects. Interestingly, there was a strong correlation between object use and object knowledge: as the degree of semantic impairment increased, the ability to use those objects decreased (see also Negri, Rumiati, et al., 2007). None of the participants presented with limb apraxia, and in subsequent tests, the participants performed within control range when asked to select and use novel tools (for similar results with a more comprehensive battery of tests, see Bozeat, Lambon Ralph, Patterson, & Hodges, 2002). Hodges and colleagues speculated that the participants with SD were able to succeed in using novel tools for a number of reasons. One factor is mechanical problem-solving, or the ability to reason about the nature of the task on the basis of visual or somatosensory features (but not learned and stored semantic information). It is not surprising that the participants with SD were able to do well in the novel tool-use task given that patients who fail the novel tool-use task tend to have lesions to fronto-parietal structures (e.g., see Hodges et al., 1999).

The Opacity of Object Affordances

A number of researchers have studied the influence of visual affordances in mediating object-use abilities in patients (e.g., see Buxbaum, Schwartz, & Carew, 1997; Hodges et al., 2000). We define affordances as the three-dimensional visual structure of the object that is interpreted in terms of motor action. Take, for example, a hammer—a hammer has a long handle that is grasped when swinging the object in order to pound nails. The handle of the hammer serves as a strong cue as to which end of the object "should" be grasped in order to functionally manipulate the tool. Thus, on the one hand, one might conclude that deriving manipulation information from the visual input of a hammer is facilitated because a hammer's correct manipulation is transparently "given" by the visual input. By contrast, the affordances of a corkscrew are perhaps more opaque in that the appropriate manipulation information is not available from the visual input alone; proper functional manipulation of a corkscrew requires the retrieval of complex manipulation knowledge from long-term memory. On the other hand, we know that even for what seems to be an object with "transparent" affordance, the manipulation knowledge is not given "bottom-up" simply from the visual input—we know this because patients with lesions to ventral stream structures (e.g., patient D.F.) have difficulty grasping objects in a functionally appropriate manner (Carey, Harvey & Milner, 1996; see also Goodale, Jakobsen, & Keillor, 1994). The fact that patient D.F. was not able to grasp objects in a functionally appropriate manner suggests that in order to appreciate even what seem to be transparent object affordances, it is necessary that the object is recognized as such.

There are also data suggesting that contextual familiarity can modulate patient performance. Snowden, Griffiths, and Neary (1994) performed a case series study of patients with SD to understand if object familiarity would modulate the patients' object- and place-naming performance. One case, K.E., could recognize and name objects that belonged to her, discussing how to manipulate the objects and where they are found in her house; however, when given the same types of objects, but exemplars that did not belong to her, K.E.'s naming performance dropped markedly, and she could not describe how to properly manipulate those objects (see also Snowden, Griffiths, & Neary, 1996).

An analogous set of issues is present in the domain of visual word reading. For example, when one reads the word *yacht*, one cannot read the letters that constitute the word *yacht* and appropriately read it as "/jɔt/"; rather, successful mapping of the letters *yacht* to the sound "/jɔt/" requires access to lexical-semantic information and subsequent lexical access (on the production side). Other words could, in theory, be read on the basis of orthography if there is transparency in the mapping of orthographic representations to phonological representations of the word, and of course languages differ dramatically in the transparency of their orthography.

The key issue for tools and novel tool-selection (or mechanical problem-solving) tasks is this: Are there familiar objects that have a truly transparent affordance structure? Or is it the case that novel tool-selection tasks simply place qualitatively different computational demands on the system than actual object use? In other words, it could be that novel tool-selection tasks are akin to developing a set of pseudoword stimuli in the context of a language with a completely opaque orthography.

Dissociations Between Manipulation Knowledge and Function Knowledge in the Healthy Brain: Evidence from Neuroimaging

Functional neuroimaging studies in healthy adults have sought to identify which regions of cortex are involved in the online computation of object function and object manipulation. Kellenbach, Brett, and Patterson (2003) asked participants to decide if a visually presented picture satisfied a manipulation-based probe question (e.g. "does using the object involve squeezing or pinching?") or a function-based probe question (e.g., "is the object used to cut?"); they also had a control condition in which participants were instructed to pay attention to scrambled photographs. Kellenbach and colleagues found that relative to the baseline condition, the left posterior middle temporal gyrus, left ventral premotor cortex, and left inferior and posterior parietal cortices were more strongly activated when making manipulation-based judgments than function-based judgments (for similar results, see Boronat et al., 2005). Canessa and colleagues (2008) replicated the pattern reported by Kellenbach and colleagues (2003) and Boronat and colleagues (2005), and in addition found that retrieval of object-based function knowledge engaged the retrosplenial cortex and lateral anterior inferotemporal cortex more so than manipulation judgments (see also Leshinskaya & Caramazza, 2015). Interestingly, the lateral and anterior portions of inferotemporal cortex are the regions of cortex that, when damaged, have been associated with impairments to function knowledge (e.g., see Hodges et al., 1999; Sirigu et al., 1991).

In two recent reports, we studied manipulation and function knowledge using multivoxel pattern analysis (Chen et al., 2016; Chen, Garcea, Jacobs, & Mahon, 2018;

see also, in this volume, Bauer & Just, Chapter 21, and Musz & Thompson-Schill, Chapter 22). In Chen and colleagues (2018), healthy adults pantomimed object use in response to word stimuli or, in separate runs, performed a difficult n-back perceptual matching task over gray-scale images of tools. Items were selected so as to be analyzable in sets of triads; for instance, one triad was "scissors, knife, pliers." Within each triad, two of the three items were related by manner of manipulation (e.g., scissors and pliers are manipulated similarly), and two of the three items were functionally related (e.g., scissors and knife are used for the same function, to cut; see Boronat et al., 2005, for precedent on this approach to structuring items experimentally). Separately, the functional magnetic resonance imaging (fMRI) volunteers also participated in a series of functional localizer scans that independently identified tool-preferring regions of interest (ROIs). Those regions, plotted in Figure 23.1, included the left inferior parietal lobule, the left and right medial fusiform gyrus, and the left posterior middle temporal gyrus.

Chen and colleagues (2016, 2018) trained a multivoxel pattern classifier (binary linear support vector machine, SVM) to discriminate the pantomime of using, for instance, a screwdriver, from the pantomiming of using scissors. The binary classifier was then tested on a new pair of items in which the manner of manipulation was similar between objects (training data: screwdriver vs. scissors; testing data: corkscrew vs. pliers). Thus, successful transfer from training to test implies decoding of manipulation information, over and above the objects themselves. Separately, the same analysis was carried out with pantomimes in which the functional properties among items were similar (training data: corkscrew vs. scissors; testing data: bottle opener vs. knife). Finally, the same types of analyses were also carried out using the n-back perceptual matching task data. Above-chance discrimination of manipulation information was observed in left motor cortex, left somatosensory cortex, and in the left anterior intraparietal sulcus. By contrast, function relations among objects could be decoded in temporal lobe regions (see also Anzellotti, Mahon, Schwarzbach, & Caramazza, 2011; Yee, Drucker, & Thompson-Schill, 2010). Perhaps the most important finding that emerged from Chen and colleagues (2018) was that the left supramarginal gyrus contained neural representations of object manipulation that transferred across object pairs (training data: screwdriver vs. scissors; testing data: corkscrew vs. pliers), stimulus format (training on words, testing on pictures, and vice versa), and task (training on pantomime testing on perceptual matching, and vice versa). These findings indicate that neural activity in the left supramarginal gyrus when participants perform tasks over tools indicate compulsory access to abstract representations of object manipulation.

Dissociations Between Manipulation Knowledge and Function Knowledge in the Healthy Brain: Evidence from Transcranial Magnetic Stimulation Studies

Recent evidence from repetitive transcranial magnetic stimulation (rTMS) studies has lent support to the hypothesis that function and manipulation knowledge constitute dissociable types of object knowledge. rTMS is a form of TMS in which high-frequency magnetic pulses are delivered to a region of cortex, extracranially, yielding a "virtual" lesion (see Schuhmann, Chapter 6 in this volume). Pelgrims, Olivier, and Andres (2011) carried out an rTMS experiment in which participants were required to decide if two visually presented objects were compatible or incompatible across four different dimensions. Pelgrims and colleagues probed manipulation knowledge by asking participants to decide if two visually presented manipulable objects were similar in the configuration of the hand when using the items (hand-configuration task), or to decide if a visually presented hand, in a specific posture (e.g., gripping), was compatible with a visually presented object (e.g., scissors; object-hand interaction task). The participants were also required to make compatibility judgments over two visually presented objects that could be used in a given context (e.g., scissors, stapler; contextual task), or for the same function (e.g., scissors, knife; function task). Pelgrims and colleagues found that rTMS to the left inferior parietal lobule (in the vicinity of the supramarginal gyrus) selectively slowed down hand-configuration judgments relative to rTMS applied to the right inferior parietal lobule, or a control site (i.e., the vertex); no differences in response time were found among the three stimulation sites when the three other tasks were carried out. Pelgrims and colleagues argued that their findings support the hypothesis that motor-based knowledge of manipulable objects is not necessary in order to access contextual/functional information about object use (for a similar argument on the basis of behavioral studies in healthy subjects, see Garcea & Mahon, 2012, and on the basis of patient evidence, see Mahon & Caramazza, 2005, 2008).

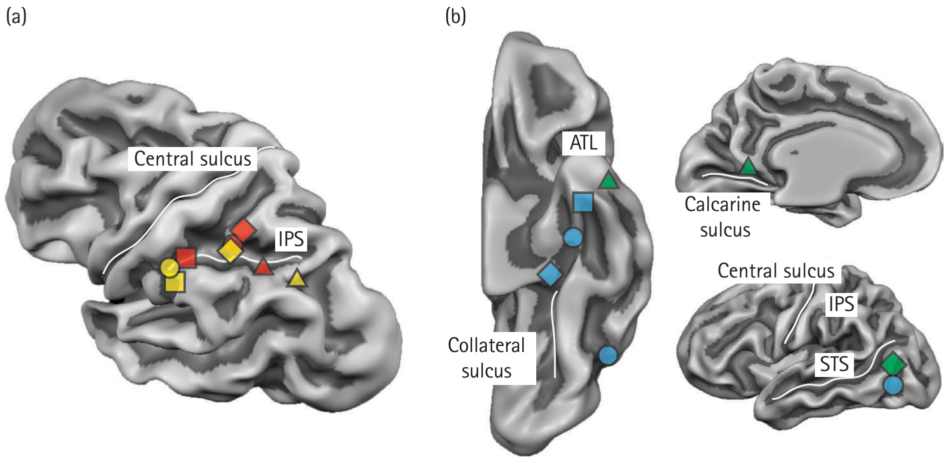
Andres, Pelgrims, and Olivier (2013) expanded on their initial rTMS findings by measuring contextual/functional and manipulation knowledge after stimulating the left inferior parietal lobule, and the left middle temporal gyrus. Andres and colleagues found that rTMS to the left inferior parietal lobule once again selectively slowed down judgments in a hand-object configuration task. Interestingly, stimulating the left middle temporal gyrus selectively slowed down judgments in the context task (e.g., are scissors and knife used in the same context?). This led Andres and colleagues to argue that the left supramarginal gyrus processes information about tools necessary to shape the hand appropriately, whereas the left middle temporal gyrus processes information relevant to the context in which the tool is typically found and used.

Ishibashi, Lambon Ralph, Saito, and Pobric (2011) combined an rTMS stimulation protocol with a semantic matching paradigm in order to understand the neural areas that contribute to function and manipulation knowledge. Participants were presented with a target word, and below that target word were three alternate words. Participants were instructed to decide which of the three alternates best matched the target word. In the function condition, the target word (e.g., *scissors*) matched the correct choice (e.g., *knife*) by function; in the manipulation condition, the target word (e.g., *scissors*) matched the correct choice (e.g., *pliers*) by manner of manipulation; the two foils were always unrelated to the target word (e.g., *whisk*). A control task employed a similar design, but required participants to make decisions about the visual similarity of scrambled pictures of words. Ishibashi and colleagues found that relative to the control task, rTMS over the left anterior temporal lobe selectively slowed down function judgments, but not manipulation judgments; in contrast, rTMS over the left inferior parietal lobule selectively slowed down manipulation judgments relative to the control task (see also Pobric, Jefferies, & Lambon Ralph, 2010). Ishibashi and colleagues argued that their results are consistent with the performance of SD patients in that rTMS to the left anterior temporal lobe slowed down judgments of tool function; and furthermore, that rTMS to the left inferior parietal lobule selectively slowed down manipulation judgments, which mirrors the performance of apraxic individuals with left parietal damage.

Function and Manipulation Knowledge in the Human Brain: Interim Summary

Taken together, there is remarkable convergence among the neuropsychological, functional neuroimaging, and TMS studies that have investigated the neural substrates of manipulation and function knowledge in the human brain. Neuropsychological studies indicate that patients with lesions to the inferior parietal lobule can be impaired for manipulating objects correctly, but spared for knowledge of objects function; in contrast, patients with temporal lobe damage can be impaired for knowledge of object function but spared for manipulating objects. After rTMS to the left inferior parietal lobule, there is interference with manipulation judgments, while function/conceptual judgments are not affected; in contrast, after rTMS applied to lateral and anterior temporal lobes, there is selective interference with conceptual/function judgments, while manipulation judgments are not affected. Figure 23.3 presents a summary of the peak Talairach coordinates of regions in the left hemisphere reported during fMRI or TMS experiments probing function and manipulation knowledge. The emerging pattern is that manipulation judgments maximally drive activity in the left parietal cortex, in the vicinity of the left inferior parietal lobule (left supramarginal gyrus, left anterior IPS); furthermore, TMS-induced transient deficits for manipulation knowledge overlap with the regions involved in processing object-associated manipulation knowledge (see Figure 23.3 A). In the context of function knowledge, online retrieval of function knowledge is associated with increased neural activity in the left ventrolateral and anterior temporal cortex, which overlaps with the regions that, when stimulated with rTMS, were associated with relative performance decrements in tasks tapping function knowledge.

The question then becomes: How do we translate this understanding of the brain regions that support manipulation and function knowledge into an understanding of how the brain deploys the right action to the right object? Imagine that your friend asks you to pass her a hammer. There is an indefinite number of ways in which you can grasp the object to pass to her—whatever is biomechanically comfortable given the physical constraints of the environment, the weight distribution



Manipulation > Function

Reference	Talairach (X Y Z)
◆ Chen et al. (2016)	−37, −44, 51
● Kellenbach et al. (2003)	−38, −41, 45
■ Canessa et al. (2008)	−49, −28, 38
▲ Boronat et al. (2005)	−37, −57, 38
◇ Ishibashi et al. (2011)*	−38, −41, 45
○ Pelgrims et al. (2011)*	−58, −30, 43
□ Andres et al. (2013)*	−59, −32, 43
△ Yee et al. (2010)	−27, −66, 23

Function > Manipulation

Reference	Talairach (X Y Z)
◆ Chen et al. (2016)	−19 −38 −12
● Yee et al. (2010)	−34 −28 −9 −43 −54 −2
■ Ishibashi et al. (2011)*	−48 −12 −15
▲ Canessa et al. (2008)	−52 −6 −30 −5 −57 −29
◆ Andres et al. (2013)*	−57 −50 4

FIGURE 23.3. Meta-analysis showing regions representing manipulation and function knowledge. (A) Peak Talairach coordinates of regions were maximally responsive when participants were asked to retrieve knowledge of object manipulation.)B) Peak Talairach coordinates of regions were maximally responsive when participants retrieved knowledge of object function. Asterisks denote studies that used TMS to measure function and manipulation knowledge. Coordinates originally published in MNI space were converted to Talairach space in order to plot all regions in a common stereotactic space.

Abbreviations: IPS: intraparietal sulcus; ATL: anterior temporal lobe; STS: superior temporal sulcus. Note that major sulci are demarcated with white lines.

of the object, and the state of your hand. However, when you pick up a hammer to use it, the reach-to-grasp interaction with the object is informed by the goal—to use the hammer according to its function—and you would grasp the hammer with a functionally appropriate grasp that anticipates its use. Consider the different ways in which one might pick up a hammer if the goal is to hammer a nail versus pull a nail out by using the claw of the hammer. Decisions that must be made over motor or visual information are causally constrained by the current behavioral goals. For instance, the retrieval of functional or manipulation knowledge is not relevant when you simply need to pass the hammer to your friend (e.g., see Creem & Proffitt, 2001; Jax & Buxbaum, 2010); however, successful use of a hammer to pound a nail requires that function knowledge is integrated with manipulation knowledge in order to satisfy the behavioral goal, and in a way that implements the designed function of the object.

It is important to emphasize that the proposal that access to object manipulation is contingent on access to object identity is not in conflict with the dorsal/ventral stream hypothesis of visual processing. The proposal that there is a dorsal visual pathway that processes online, visual information in the service of action never claimed that access to complex object-associated manipulation is given by the dorsal stream. In other words, manipulation knowledge is not given by a "bottom-up" analysis of the visual input devoid of semantic interpretation; rather, volumetric analysis of an object in a semantically uninterpreted manner is the provenance of the dorsal visual pathway (e.g., see Almeida et al., 2008; Almeida et al., 2014). These issues are at times run together in the literature, where "parietal" activity is considered to be "activity in the dorsal stream," rather than simply access to action information potentially entirely contingent on prior retrieval of object-identity information in the ventral visual pathway. Where the current proposal does substantively interface with the dorsal/ventral stream hypothesis is in the context of functionally appropriate object grasping. The dorsal stream would not know, on its own, how to grasp an object in a functionally appropriate manner; in order to grasp an object in a functionally appropriate manner, it is necessary to retrieve cognitive or semantic information about what the object is and what its function is, in a manner that is integrated with current behavioral goals. What this suggests is that the dorsal stream may provide a "space" of possible object-directed grasps and that parietal regions then look to information yielded via a ventral stream analysis in order to winnow that space down to the space of functionally appropriate grasps (for discussion, see Mahon and Wu, 2015; Garcea et al., in press).

The data reviewed to this point converge on the idea that computation of object identity and retrieval of object function occur via ventral stream pathways, and that access to manipulation knowledge in the left inferior parietal lobule is contingent on prior analysis of the object by the ventral visual pathway (for relevant findings, see Almeida et al., 2013; Garcea et al., 2016; Kristensen et al., 2016; Mahon et al., 2013; for discussion, see Binkofski & Buxbaum, 2013). Furthermore, in order to deploy functionally appropriate grasps to objects, it is necessary to take into account the eventual manipulation to be applied to the object once it is in hand, and that retrieval of manipulation information presupposes the retrieval of information about object identity and function. Thus, understanding how functionally appropriate grasps are deployed to objects may point toward a deeper understanding of interactions between the ventral and dorsal visual pathways (e.g., Creem-Regher & Lee, 2005; Goodale et al., 1994; Wu 2008). An important first step in addressing that hypothesis is to identify the structural and functional connectivity between regions of cortex that could, in principle, integrate action-relevant processing in parietal cortex with cognitive or semantic analysis of objects in the ventral stream.

ANATOMICAL AND FUNCTIONAL CONNECTIVITY IN THE TOOL-PROCESSING NETWORK: TOWARD A NEW FRAMEWORK FOR UNDERSTANDING IMPAIRMENTS FOR OBJECT USE

There is a rich literature parcellating parietal cortex on the basis of sulcul and gyral structural similarity (e.g., Caspers, Geyer, Schleicher, Mohlberg, Amunts, & Zilles, 2006), nonhuman primate tract tracing (e.g., see Borra, Belmalih, Calzarava, Gerbella, Murata, Rozzi, et al., 2008; Borra, Ichinohe, Sato, Tanifuji, & Rockland, 2010), autoradiographic labeling (e.g., see Pandya & Seltzer, 1982), neurotransmitter receptor density (e.g., see Caspers, Schleicher, Bacha-Trams, Palomero-Gallagher, Amunts, et al., 2013), white matter connectivity (e.g., see Caspers, Eickhoff, Rick, von Kapri, Kuhlen, et al., 2011; Mars, Jbabdi, Sallet, O'Reilly, Croxson, Olivier, et al., 2011; Ruschel, Knösche, Friederici, Turner, Geyer, & Anwander, 2014; Rushworth, Behrens, & Johansen-Berg, 2006), and more recently, functional connectivity (e.g., see Garcea & Mahon, 2014). Studies have focused on parcellating the inferior parietal lobule (Caspers et al., 2006; Caspers et al., 2011; Caspers et al., 2013; Ruschel et al., 2014; Zhong & Rockland, 2003), the superior parietal lobule (Zhang, Fan, Zhang, Wang, Zhu, et al., 2014), or the entire parietal lobe (Durand, Nelissen, Joly, Wardak, Todd, et al., 2007; Mars et al., 2011; Nelson, Cohen, Power, Wig, Miezin, et al., 2010; Orban, Claeys, Nelissen, Smans, Sunaert, et al., 2006; Rushworth et al., 2006; for review, see Kravitz, Saleem, Baker, & Mishkin, 2011).

Caspers, Schleicher, Bacha-Trams, Palomero-Gallagher, Amunts, and Zilles (2013) have recently argued for a parcellation scheme on the basis of autoradiographic labeling of neurotransmitter receptors carried out in post-mortem brains. Caspers and colleagues showed that the inferior parietal lobule could be parcellated into three clusters: the first cluster was positioned in the rostral portion of the inferior parietal lobule (areas PFop, PFcm, and PFt); the second cluster was positioned in an intermediate area between the supramarginal gyrus and angular gyrus (areas PF and PFm); the third cluster was positioned in the lateral and posterior portion of the inferior parietal lobule (posterior PG [PGa and PGp]; see Caspers et al., 2013, Figure 8 D therein). This parcellation of the inferior parietal lobule aligns well with previous parcellations of the inferior parietal lobule (e.g., see Caspers et al., 2006; Caspers et al., 2011), and with human and nonhuman primate studies parcellating parietal cortex by its white matter connectivity and resting-state connectivity (e.g., see Mars et al., 2011; Rushworth et al., 2006).

While some studies have focused on the organization of the subregions within the inferior parietal lobule (e.g., see Caspers et al., 2006; Caspers et al., 2011; Caspers et al., 2013; Mars et al., 2011; Rushworth et al., 2006), others have measured the whole-brain cortical connections of the inferior parietal subregions. For example, Borra, Belmalih, Calzarava, Gerbella, Murata, Rozzi, et al. (2008) used tracer injections in the macaque brain to measure the connections of the anterior intraparietal sulcus (aIPS). The anterior intraparietal sulcus processes visuomotor information in order to shape the hand to grasp objects in the environment (e.g., see Binkofski, Buccino, Posse, Seitz, Rizzolatti, & Freund, 1999; Binkofski, Dohle, Posse, Stephan, Hefter, Seitz, et al., 1998; Sakata, Taira, Murata, & Mine, 1995). Borra and colleagues found that regions of premotor cortex (F5) in the macaque brain receive inputs from the anterior intraparietal sulcus, in the vicinity of area PF (see also Rizzolatti & Matelli, 2003); they also found that the anterior intraparietal sulcus receives inputs from the lateral superior temporal sulcus and regions within the middle temporal gyrus and ventral temporal cortex (see also Borra et al., 2010; Zhong & Rockland, 2003).

Garcea and Mahon (2014; see Figure 23.4) sought to integrate what is known about the anatomical connections of the inferior parietal lobule with an analysis of functional

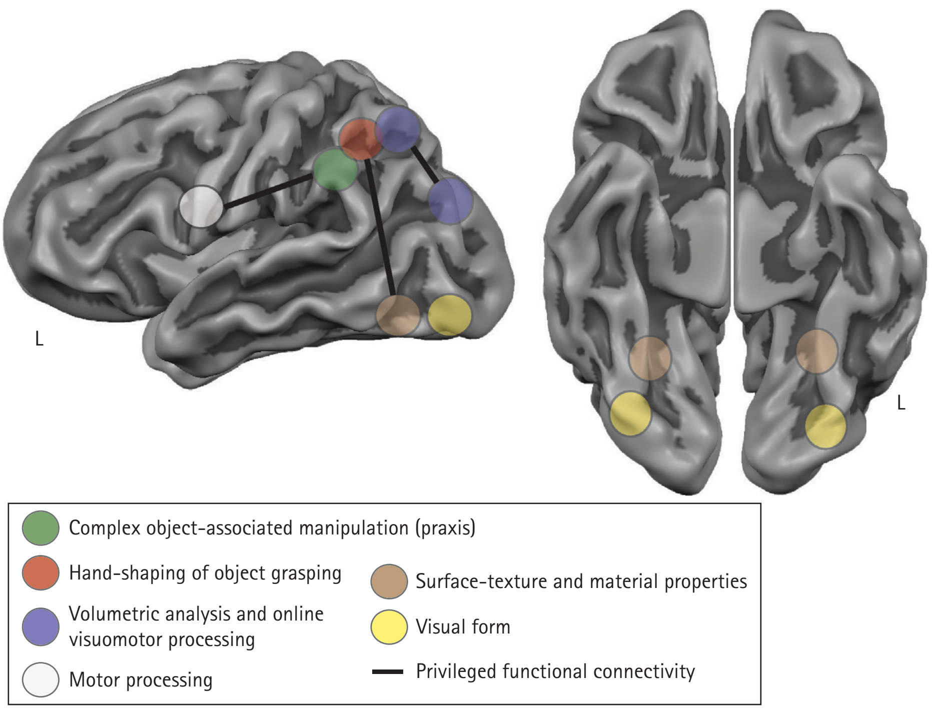

L
L
🟢 Complex object-associated manipulation (praxis)
🔴 Hand-shaping of object grasping
🔵 Volumetric analysis and online visuomotor processing
⚪ Motor processing
🟤 Surface-texture and material properties
🟡 Visual form
— Privileged functional connectivity

FIGURE 23.4. A network perspective on tool processing in the human brain. The key finding is that left parietal tool preferring voxels can be triply dissociated (using k-means clustering) based on their functional connectivity to frontal motor areas, temporal lobe object-processing areas, and dorsal occipital regions involved in object-directed reaching. Privileged functional connectivity among tool representations in the brain supports the integration of complex object-associated manipulation knowledge with representation of object identify and form, which is sent to the frontal-motor cortex for subsequent motor output.

Source: Derived from Garcea and Mahon (2014) with permission.

connectivity among parietal, temporal, and frontal-motor tool-preferring regions in the human brain. In their analysis, Garcea and Mahon parcellated the tool-selective left parietal cortex into three clusters on the basis of differential functional connectivity to tool-selective regions in the motor system (left ventral premotor cortex), temporal lobe (left medial fusiform gyrus, left posterior middle temporal gyrus), and dorsal stream (left dorsal occipital cortex). Ventral premotor tool-preferring areas expressed privileged functional connectivity the lateral and inferior parietal cortex (for similar results using white matter connectivity, see Caspers et al., 2011; Mars et al., 2011; Ruschel et al., 2014; Rushworth et al., 2006); the left medial fusiform gyrus and left posterior middle temporal gyrus expressed privileged functional connectivity with the anterior intraparietal sulcus (for convergent findings using functional connectivity, see Almeida et al., 2013; Mahon et al., 2007; Mahon et al., 2013; Stevens, Tessler, Peng, Martin, 2015; for review of white matter connectivity results, see Kravitz et al., 2011); the left dorsal occipital cortex expressed privileged functional connectivity to the superior parietal tool preferring area.

As noted earlier, neuropsychological evidence indicates that damage to the left inferior parietal lobule is associated with limb apraxia, while damage to the superior and posterior parietal lobule is associated with optic ataxia. One speculation that may be extrapolated from prior research that sought to parcellate parietal cortex based on anatomical and functional connectivity is that some forms of limb apraxia may be attributable to a disconnection deficit in which parietal action representations are de-afferented of inputs from temporal lobe representations of object concepts or from frontal-motor areas. Geschwind (1965) proposed a similar approach to understanding the causes of apraxia. In his model, Geschwind suggested that the variants of limb apraxic errors could be traced back to a differential disconnection among visual, motor, and left hemisphere language areas that process information relevant for action production.

This framework predicts that disconnection of parietal action representations from temporal lobe representations of object concepts could result in errors of content in object use. In so-called ideational apraxia, patients' movements are kinematically and spatially coherent, but are carried out with the incorrect objects—for instance, using a toothbrush as if it were a knife. In contrast, disconnecting left parietal action representations from frontal motor areas would, by hypothesis, give rise to actions that are conceptually correct, but spatially and kinematically incorrect—for instance, a toothbrush would be used in the correct context, but the organization of the fingers and joints would be spatially incoherent and kinematically incorrect (see also Binkofski & Buxbaum, 2013).

CONCLUSION

On a daily basis we perceive, recognize, grasp, and use tools—we do this effortlessly and fluidly in the service of behavioral goals. The "ability to recognize and use tools" is a complex set of processes spread across many domains of cognition, and tool use in humans has a widely distributed neural basis. This means that in order to understand how the brain accesses action information from visual input, it is necessary to understand what types of information about objects are computed by each of the distinct pathways that "connect the eyes to the hands" and the "eyes to the mouth." The goal of this short review has been to review evidence from three sources—functional neuroimaging, neuropsychological studies of brain damaged patients, and TMS perturbations of the healthy brain—that collectively bear on the issue of how manipulation and functional knowledge about objects are organized and represented in the brain. As we have briefly reviewed, a tremendous amount of progress has been made in advancing our understanding of how object-directed actions in the parietal lobe interface with high-level visual representations in the temporal lobe and with the frontal-motor system.

We would suggest that many of the key issues that lay ahead of us, as a field, are summarized by this question: How does the brain figure out how to deploy the correct actions to the correct objects? We don't pick up a banana to call our friend, or use a toothbrush to clean the sink—why not? How can the errors exhibited after focal brain injury constrain our understanding of the structure and dynamics of the system that interfaces semantic and cognitive representations of objects and actions with action-relevant representations that mediate our physical interaction with the world? Progress on these questions requires a computational theory (in the sense of Marr, 1982), and such a computational theory requires explicit bridging hypotheses about how it may be implemented in neural architecture (for cogent discussion in the domain of language, see Poeppel, 2012).

One exciting and new direction for the field is to analogize more aggressively from models of lexical access to models of action processing; the theoretical contribution of Rothi, Ochipa, and Heilman (1991) was foundational in establishing a cognitive framework within which to think about how the correct actions are deployed to the correct objects. In the more than 25 years since their proposal, we would suggest that while much progress has been made in terms of understanding the neural correlates of object-directed action processing, the basic parameters of a cognitive model proposed by Rothi and colleagues remain the state of the art. This may of course be because the model works and there have been no findings that dramatically challenge its core components (for an extension on the original proposal by Rothi et al., 1991, see Cubelli et al., 2000). Perhaps further progress could be spurred by taking a more granular approach to understanding the basic building blocks of complex object-associated actions. For instance, it is an open empirical question whether a complex action such as using a corkscrew could be decomposed into elemental components, such that there are shared "primitives" with other actions (many with the action of using a screwdriver, fewer with the action of turning a doorknob, fewer still with the action of brushing one's teeth). In other words, are "units" of action-representations recombined to form larger complex actions, or are complex actions represented holistically and, as such, non-decomposable? If action representations were shown to be componentially built from smaller units, then an exciting direction would be to begin to ask what the "syntactic" computations are that operate over those granular representations, and whether fine-grained connectivity can relate specific object affordances to those action primitives. In summary, we suggest that a fruitful direction may be to adopt the approach taken by models of lexical access, in which there has been concerted focus on understanding the granularity of representations at each level of processing, the computations applied to those representations, the connectivity of those representations across and within levels, and the processing dynamics that mediate system-level processing.

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CHAPTER 24

NEURAL BASIS OF MONOLINGUAL AND BILINGUAL READING

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The use of printed symbols to represent the world is a unique human activity. Compared to oral communication, writing and reading are very recent abilities in the history of human evolution, emerging approximately about 4,000–5,000 years ago. The first known systems of writing were pictographs and counting methods used in commerce in 3,200 B.C.E. (Spar & Lambert, 2005). In addition to the evolution of written symbols, social expectations and assumptions about reading correspondingly evolved (Finkelstein & McCleery, 2012). In this regard, those individuals who could read held considerable economic and social importance (Moorhead, 2011). This made reading not only a very useful activity, but also an important social ability that probably contributed to its expansion. Currently, reading has become an elementary part of our modern society, so that we are continually exposed to written messages in media (e.g., television, advertising messages on the street, etc.) and also in technologies (e.g., computers, mobile phones).

Nonetheless, reading is not a simple process; it involves a series of sequential/parallel and mutually dependent cascades of neurocognitive operations. Reading requires first the visual recognition of a word or a symbol and the correspondence between this visual form and its phonology. Furthermore, alphabetic writing systems require an awareness of the phonological constituents that make up the word. This awareness allows the reader to connect letter strings (i.e., orthography) to the corresponding units of speech (i.e., phonology). Moreover, reading requires accessing the meaning of those words (i.e., semantics). Thus, typical reading relies on a progressive interaction between visual, orthographic, phonological, and semantic systems. The use of advanced neuroimaging techniques (see the chapters in Part I of this volume) allows researchers to examine in vivo the neural correlates underlying these operations. Better understanding of the neural dynamics supporting reading is a priority for cognitive neuroscience, with profound implications for elucidation of the brain mechanisms supporting typical and atypical reading (i.e., reading disorders), as well as to contribute to improving educational policies.

The amount of research dedicated to understanding the neural correlates of reading has steadily increased over the last two decades. A PubMed search using “reading” and “MRI” as combined terms reveals over 3,100 peer-reviewed journal articles published between 1996 and 2016. A detailed analysis indicates that the main goals of these studies were to examine brain processes associated with orthographic, phonological, and/or semantic systems embedded in written material. However, whereas some of these studies focused on regional specialization or examined the contribution of specific regions, more recent studies have followed a network-based approach or combined regional- and network-based approaches.

The present chapter is aimed at reviewing what is known about the neural bases of reading in monolingual and bilingual populations. Specifically, the first section reviews empirical evidence on the functional specialization of left perisylvian reading regions and their participation in orthographic, phonological, and semantic reading systems, paying special attention to current theoretical debates on the functional role of these main reading nodes. Second, we present an overview of the ventral and dorsal reading networks and the factors that seem to modulate them, including the type of stimuli, reading demands, and language orthography. Finally, the third section of the chapter pays particular attention to the neural correlates underlying bilingual reading and reviews research evidence showing that age of acquisition, language proficiency, language exposure, and language orthography modulate the engagement of reading regions and networks in bilinguals.

FUNCTIONAL SPECIALIZATION OF LEFT PERISYLVIAN READING REGIONS

Empirical evidence has demonstrated that reading is mediated by a dedicated cortical network, located along the perisylvian areas of the left hemisphere (e.g., Carreiras, Mechelli, Estévez, & Price, 2007; Jobard, Crivello, & Tzourio-Mazoyer, 2003). As illustrated in Figure 24.1, four different large brain areas can be identified within this network: the inferior frontal gyrus (including *pars opercularis, triangularis*, and *orbitalis*), middle and superior temporal gyrus, parietal cortex, and ventral occipito-temporal cortex (Jobard et al., 2003; Sandak et al., 2004). Researchers have long debated the role played by these key language-related regions in reading tasks involving orthographic, phonological, and semantic processing (Schlaggar & McCandliss, 2007), and despite some differences in terms of results and theoretical views about the roles of some of

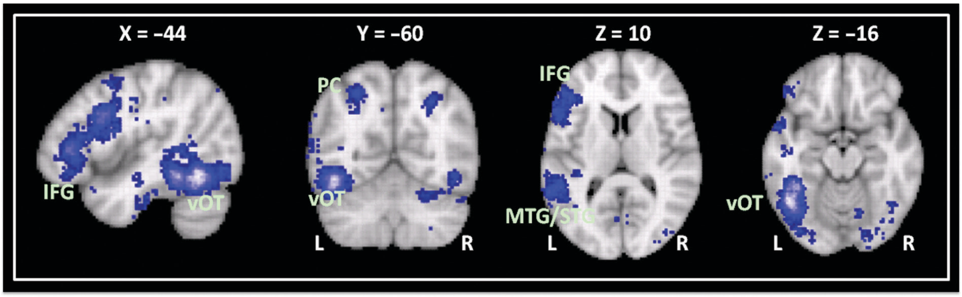

FIGURE 24.1. Meta-analysis of fMRI activations associated with the term "reading" in a total of 427 studies. Regions in blue represent areas that are reported more selectively with the term reading (reverse inference, $Z = 1.96$).

Abbreviations: IFG = inferior frontal gyrus; MTG/STG = middle/superior temporal gyrus; PC = parietal cortex; vOT = ventral occipito-temporal cortex; L = left hemisphere; R = right hemisphere.

Source: Results from Neurosynth.org (Yarkoni, Poldrack, Nichols, Van Essen & Wager, 2011).

these regions, neuroimaging research has been seminal in understanding their overall contribution to reading processes at regional and network levels.

Inferior Frontal Gyrus

The left inferior frontal gyrus (IFG) has been indicated as a key component of reading (Price, 2012). Empirical evidence has shown the engagement of this region in word reading (Mechelli, Price, Friston, & Ishai, 2004), lexical and semantic retrieval (Binder, Desai, Graves, & Conant, 2009; Carreiras, Mechelli, & Price, 2006), and mapping orthography to semantics (Jobard et al., 2003).

The IFG can be divided into its anterior-ventral (*pars orbitalis* and *pars triangularis*), and posterior-dorsal parts (*pars opercularis*). These ventral and dorsal subdivisions are mainly based on cytoarchitectonic and neuroanatomical studies conducted over the twentieth century. One of the first cytoarchitectonic differentiations of the anterior and posterior parts of the human IFG was proposed by Brodmann (1909). Specifically, there are variations between anterior and posterior parts of the IFG in size and packing density of cell bodies over the layers of the cortical sheet. Brodmann's initial division of the IFG was further refined by comparative neuroanatomical studies between monkey and human brains (Economo & Koskinas, 1925; Petrides & Pandya, 1994, 2002; Walker, 1940; see Petrides, Tomaiuolo, Yeterian, & Pandya, 2012, for a review). Moreover, other parameters were added successively to this initial topological classification, such as the distribution and amount of intra-cortical myelinated fibers (Vogt, 1910), precise axonal terminations in IFG parts in the macaque brain (Petrides & Pandya, 2009), density of certain neurotransmitters receptors (Zilles, Palomero-Gallagher, & Schleicher, 2004) and resting-state functional connectivity in humans based on the macaque monkey data (Kelly et al., 2010).

Consistently, recent neuroimaging studies on reading have found a differential functional involvement of anterior-ventral and posterior-dorsal IFG regions (e.g., Badre & Wagner, 2007; Price, 2012). Specifically, the anterior IFG is more strongly engaged in studies using semantic reading tasks and when word retrieval during the reading task is semantically demanding, such as retrieving narratives (Badre & Wagner, 2002, 2004; De Zubicaray, Wilson, McMahon, & Muthiah, 2001; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). In contrast, when stronger phonological demands are required by the task, for example during a rhyming task, stronger posterior IFG engagement is typically found (Bitan et al., 2005; Gabrieli, Poldrack, & Desmond, 1998; Poldrack et al., 1999). Structural and functional neuroimaging evidence has also highlighted the critical role of the interactions between IFG and lateral temporal cortex during reading, with different parts of the left IFG orchestrating controlled retrieval of lexical/semantic representations from lateral posterior temporal cortex via top-down processes (e.g., Badre & Wagner, 2007; Hagoort, 2013; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; see also Molinaro, Paz-Alonso, Duñabeitia, & Carreiras, 2015).

Middle/Superior Temporal Gyrus

Neuroscientific reading models have agreed on the participation and roles of the IFG and posterior middle/superior temporal gyrus (MTG/STG) in reading processes (e.g., Friederici, 2012; Hagoort, 2013; Lau, Phillips, & Poeppel, 2008; Snijders, Petersson, & Hagoort, 2010; see also Brouwer & Hoeks, 2013; Jefferies, 2013). In most of these models, accessing lexical/semantic information related to single words is associated with posterior MTG/STG activation. Neuroimaging and neuropsychological research have also shown the involvement of these posterior temporal regions in tasks that require judgments on word semantic properties, semantic categorizations, or lexical semantic processes (e.g., Cappa, Perani, Schnur, Tettamanti, & Fazio, 1998; Price et al., 1994; Pugh et al., 1996). Furthermore, aphasic patients with lesions in these posterior temporal regions have difficulties performing semantic tasks that require access to lexical representations (e.g., Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Hart & Gordon, 1990).

Parietal Cortex

The specific role of the parietal cortex in reading processes has long been debated. Empirical evidence has shown that different regions within the parietal cortex are associated with different language functions. Whereas some studies have highlighted the overall involvement of parietal regions in phonological processing, others have pointed out that certain regions within the parietal cortex are involved in semantic processes. One the one hand, previous studies have suggested the involvement of the supramarginal gyrus (SMG) in phonological reading processes (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012), such as assembled phonology or grapheme-to-phoneme mapping (Graves, Desai, Humphries, Seidenberg, & Binder 2010; Mei et al., 2014; Mei et al., 2015), processing phonological versus processing semantic information (e.g., Devlin et al., 2003; Seghier et al., 2004), and reading aloud pseudowords versus words (e.g., Binder, Medler, Desai, Conant, & Liebenthal, 2005; Carreiras, Duñabeitia, & Perea, 2007; Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005). On the other hand, the angular gyrus is typically involved in semantic processing of auditory and visual stimuli (Demonet et al., 1992; Molinaro et al., 2015; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996), a finding that has been extensively and reliably replicated across multiple studies with different semantic tasks and stimuli (e.g., Binder et al., 2009; Cabeza & Nyberg, 2000; Quiñones et al., 2014; Vigneau et al., 2006).

Importantly, the left angular gyrus and SMG can be parcellated into multiple functionally different subregions. For instance, Seghier et al.'s (Seghier, Fagan, & Price, 2010) study characterized three functional subdivisions in the left angular gyrus differentially related to semantic processing and processes related to the default-network. Similarly, Oberhuber et al.'s (2016) study found four functionally distinct regions, all within left SMG, that have implications for differentiating between different types of phonological processing operations, including articulatory sequencing, auditory processing, word production, and executive functioning. Thus, even within these parietal cortex regions, there are relevant differences with regard to the specific functional contributions of their subregions.

Interestingly, some recent findings have also highlighted the role of parietal regions in the early stages of visual word recognition, suggesting that these areas contribute to letter-identity and letter-position processing. For instance, Reilhac, Peyrin, Démonet, and Valdois (2013) reported increased activity in the left superior and inferior parietal cortex during processing of two consecutive five-letter strings that could differ in the replacement of some internal characters (e.g., TSHFL-TSHFL versus TSHFL-TGHML). In addition, Carreiras, Quiñones, Hernádez-Cabrera, and Duñabeitia (2014) manipulated character-position and character-identity through the transposition or substitution of two internal elements within strings of four letters, digits or symbols (e.g., letters: NDTF-NTDF vs. NDTF-NKSF; digits: 1754-1574 vs. 1754-1684; symbols: &$?<-&?$< vs. &$?<-&%€<). In this study, participants were asked to decide whether the two subsequent strings were the same or different. Critically, these authors showed a dissociation effect for letters versus digits and symbols, both relative to the letter-identity and letter-position coding processes. In particular, the left inferior and superior parietal gyri showed increased activation for letter strings as compared to the other types of characters. Moreover, common effects of transpositions for all types of characters were found in the right inferior and superior parietal and in the right angular gyrus, but at the same time differential effects for letters as compared to digits and symbols were found, with letter-specific effects in the left superior and inferior parietal cortex. These studies highlight the importance of the parietal cortex in perceptual tasks that involve letter identification, and suggest that parietal regions may be involved in the early stages of visual processing.

Ventral Occipito-Temporal Cortex

The left ventral occipito-temporal cortex (vOT) plays a crucial role in reading and has been proposed as a core area for orthographic processing during visual word recognition. This region has been proposed as the gateway from vision to language, where visual word recognition occurs prior to accessing nonvisual information (Twomey, Kawabata Duncan, Price, & Devlin, 2011). This region exhibits a marked preference for letter strings with orthographic information, showing higher activation for words and pseudowords relative to false fonts or checkerboards (e.g., Baker et al., 2007; Cohen et al., 2002; Binder, Medler, Westbury, Liebenthal, & Buchanan, 2006). However, critically, the preferential left vOT engagement for visual orthographic processing, its functional selectivity, as well as its functional role during reading, are still subjected to important debates (e.g., Carreiras, Armstrong, Perea, & Frost, 2014; Dehaene & Cohen, 2011; Price & Devlin, 2011).

Some theoretical accounts highlight left vOT involvement in bottom-up pre-lexical computation processes of visual word forms (Dehaene & Cohen, 2011; Cohen et al., 2000), while others underline its implication in integrating visuospatial features abstracted from sensory inputs with higher-level associations via bottom-up and top-down connections (i.e., interactive account; Price & Devlin, 2011). Nevertheless, differences in terms of reading paradigms and analytical approaches can potentially contribute to these divergences with regard to the putative functional role of this region in reading (Glezer & Riesenhuber, 2013). First, whereas studies supporting a pre-lexical computational role of the vOT have mainly used low-level reading tasks (e.g., passive silent reading; Cohen et al., 2002; Dehaene et al., 2010; Pegado, Nakamura, Cohen, & Dehaene, 2011), most of the studies favoring the interactive account of the vOT have typically utilized high-level reading tasks (e.g., lexical decision; Seghier & Price, 2013; Twomey et al., 2011; Woollams, Silani, Okada, Patterson, & Price, 2011). Second, there is a strong inter-subject variability in the location of the left vOT, probably due to its rapid readaptation to support a phylogenetically new skill (Bouhali et al., 2014; Dehaene & Cohen, 2011), and differences in how this region is neuroanatomically identified in different studies can also determine different results and interpretations about its role. For instance, Glezer and Riesenhuber's (2013) study revealed that the left vOT showed word selectivity when it was identified at the individual-subject level, but inter-subject variability when the vOT was identified at the group level or was based on coordinates from previous studies caused this selectivity to be washed out.

A recent functional magnetic resonance imaging (fMRI) study (Oliver, Carreiras, & Paz-Alonso, 2017) investigated differences in left vOT as a function of perceptual (i.e., to identify words that contained a colored letter) versus semantic (i.e., to identify any words that were the name of an animal) demands on reading, additionally using different strategies to identify this region: individual-subject level, group level, and coordinates from previous studies (see Figure 24.2). Results revealed that semantic reading demands relative to perceptual reading demands elicited stronger recruitment of the left

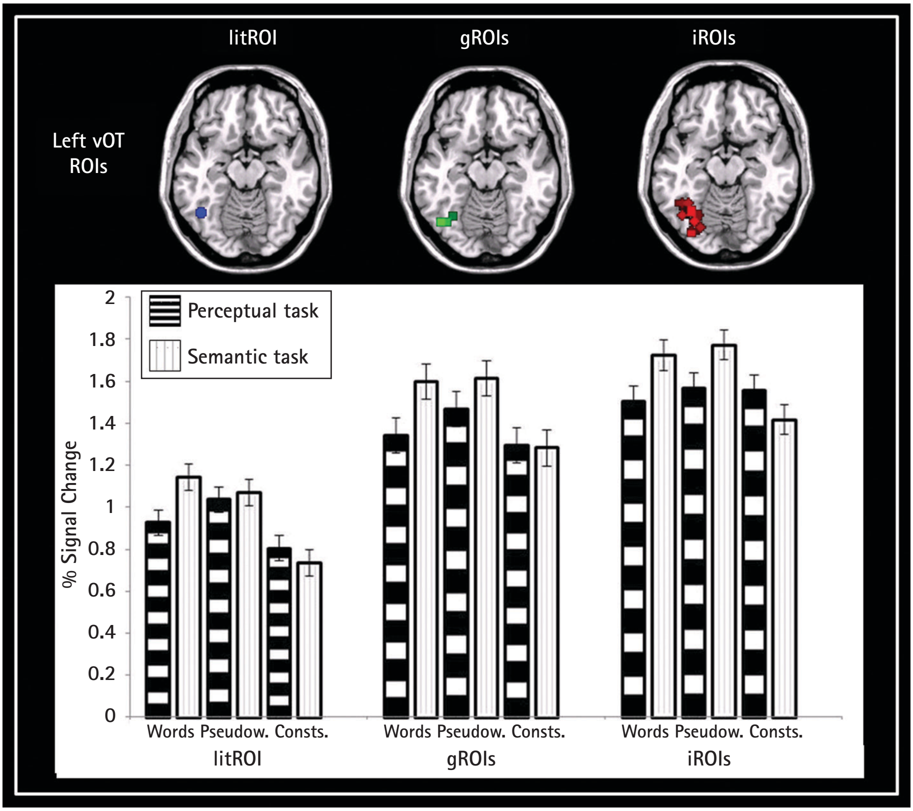

FIGURE 24.2. Left vOT ROI analyses based on three different approaches: literature-based ROI (litROI), group-based ROIs (gROIs), and individually defined ROIs (iROIs). Bar graphs show averaged parameter estimates (% signal change) for these three left vOT ROI definitions as a function of words, pseudowords, and consonant string stimuli.

Abbreviations: Pseudow. = pseudowords; Consts. = consonant strings.

Source: Modified with permission from Oliver et al. (2017).

vOT. Thus, low- versus high-level reading demands may modulate differences typically observed with regard to the functional role of left vOT in previous studies.

Dorsal and Ventral Reading Networks

Based on behavioral evidence, two main theoretical models have been proposed to explain reading processes: the parallel distributed processing (PDP) model (Harm & Seidenberg, 1999; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989), and the dual route cascaded (DRC) model (Coltheart, Rastle, Perry, Langdon & Ziegler, 2001). Although these models have put forward relevant hypotheses about how the orthographic, phonological, and semantic systems are divided and interrelated to each other, they did not provide specific predictions in relation to the neural computations carried out by the left perisylvian reading regions. However, in line with these models, neuroimaging research has been important in elucidating a division of labor between brain regions, organized into ventral and dorsal reading neural networks. Research evidence has shown that the ventral reading network, including left vOT and anterior IFG (*pars orbitalis* and *pars triangularis*), supports mapping of orthographic-lexical stimuli onto semantic representations (Sandak et al., 2004). On the other hand, the dorsal reading network, encompassing parietal cortex, STG, and posterior IFG (*pars opercularis*), is thought to subserve the link between the orthographic form of words and semantics via phonological processing (Pugh et al., 2001; Schlaggar & McCandliss, 2007).

Investigating visual word recognition involves establishing links between the processing of visual features, and semantic and phonological processing on these ventral and dorsal streams. Evidence of semantic and phonological reliance on ventral and dorsal pathway regions comes from studies revealing a specific modulation of these two pathways based on the type of stimuli and reading demands. Regarding the type of stimuli, ventral regions typically show greater engagement for high-frequency words than for pseudowords (Jobard et al., 2003; Vigneau et al., 2005), which suggests that the ventral pathway is recruited for well-learned words and is involved in more automatic word identification (Jamal, Piche, Napoliello, Perfetti & Eden, 2012). In contrast, dorsal regions typically show stronger activation during reading pseudowords and low-frequency words (Borowsky & Besner, 2006; Mechelli, Gorno-Tempini, & Price, 2003; Tagamets, Novick, Chalmers, & Friedman, 2000). The increased activation for pseudowords in regions along the dorsal stream may reflect demands on accessing phonology from sub-lexical orthographic codes (Price, 2012). Concerning reading demands, ventral regions appear to be more strongly activated by semantic than phonological reading tasks (Price & Mechelli, 2005). In contrast, the opposite pattern is found in dorsal regions, which are typically more activated for phonological than semantic reading-related decisions (Paulesu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992).

Importantly, different languages present different writing systems, and therefore reading demands may differ depending on the characteristics of a given language. Neuroimaging studies have revealed a different modulation of these ventral and dorsal reading pathways depending on the orthography of the language (Oliver et al., 2017; Paulesu et al., 2000; Rueckl et al., 2015). Languages can be classified according to their grapheme-to-phoneme mapping or language orthography (Frost, Katz, & Bentin, 1987). Transparent orthographies, such as Spanish or Italian, have a shallow letter-to-sound correspondence. Opaque orthographies, such as English, have a more complex grapheme-to-phoneme mapping. Given that transparent orthographies have relatively simple, consistent, and complete connections between letters and phonemes, it is easier for readers to recover the phonology of the printed words pre-lexically, by assembling grapheme-to-phoneme correspondences. In other words, the phonology of transparent orthographies directly supports word-recognition processes. In contrast, in opaque orthographies, the reader must process printed words by referring to their morphology via the visual-orthographic structure of the printed words (Frost et al., 1987; Pugh et al., 2001).

Neuroimaging evidence has shown that whereas transparent languages rely more on phonological areas within the dorsal pathway, opaque orthographies rely more on ventral pathway regions—consistent with graphemic analysis, to resolve possible ambiguities with pronunciation (Meschyan & Hernandez, 2006; Paulesu et al., 2000). However, the opposite pattern was also found in another study (Jamal et al., 2012), suggesting that if less phonological processing is needed, as would be expected in transparent languages, there may be less use of the phonological (dorsal) pathway and greater use of the semantic (ventral) pathway. In contrast, in opaque languages, greater activation of the dorsal route would be expected. Further studies on language orthography are needed to resolve these mixed findings.

In a recent fMRI study intended to examine the overlap between speech and reading networks across languages varying in orthographic depth and in writing system (i.e., Spanish, English, Hebrew, Chinese), Rueckl et al. (2015) found that a striking convergence emerged as a common brain signature across the wide spectrum of selected languages. This speech-print convergence may reflect a universal principle of brain organization resulting from the biological constraints imposed by initial perisylvian specialization for speech and natural-language processing, and the cognitive imperative to leverage these biologically specialized systems for supporting reading comprehension across highly contrastive languages such as Spanish and Chinese. Importantly, Rueckl et al.'s (2015) study also revealed a higher speech-print correlation among regions along the dorsal reading network for transparent (i.e., Spanish) versus opaque orthographies (i.e., English and Hebrew), including left SMG/inferior parietal lobe (IPL) and left IFG. In contrast, speech-print correlations were higher for these opaque orthographies compared with transparent orthography in left angular gyrus, left posterior MTG, left vOT, and left *pars triangularis* in the IFG (see Figure 24.3). Results from this study are especially relevant to the debate about language orthography effects in ventral and dorsal reading networks. Although there has been extensive discussion about how orthographic depth modulates the reading networks, most of this previous work comes from behavioral research (Caravolas et al., 2012; Caravolas, Lervåg, Defior, Málková, & Hulme, 2013; Frost et al., 1987; Ziegler et al., 2010) and the few available functional neuroimaging studies on this topic have been typically limited to two-language comparisons (e.g., Cherodath & Singh, 2015). Moreover, Rueckl et al.'s (2015) work constitutes the first study that has specifically examined speech-print convergence, showing that sites with stronger speech-print coupling in orthographically transparent systems such as Spanish are generally associated with phonological processing, whereas the sites with stronger speech-print coupling in orthographically deep systems such as English and Hebrew (including angular gyrus, MTG, and ITG) are more closely associated with semantic processing.

Additional support showing the different types of decoding required during the reading process as found in fMRI studies on the ventral and dorsal functional pathways

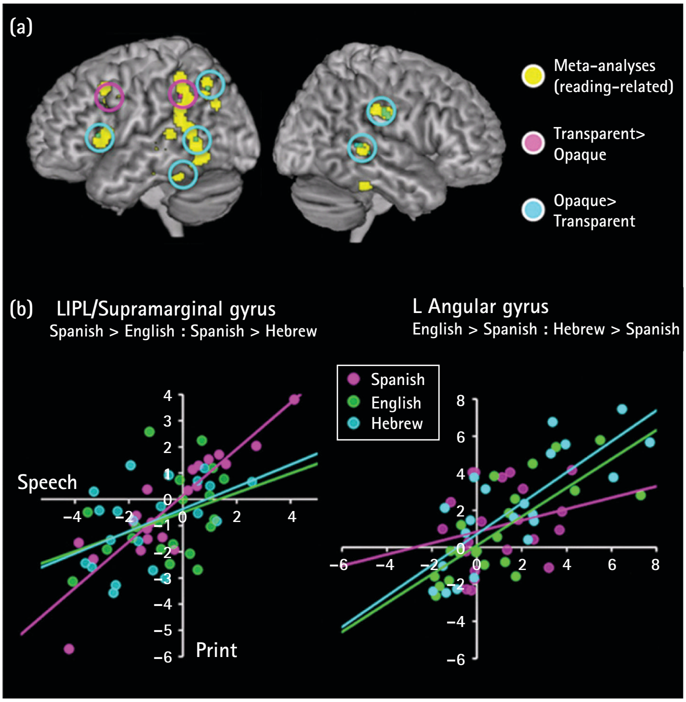

FIGURE 24.3. Speech-print convergence as a factor of orthographic depth in three contrastive alphabetic languages. (A) Areas in yellow show the reading circuit identified by published meta-analyses. Speech-print correlations were higher for transparent (Spanish) than opaque orthographies (English and Hebrew compared independently, $P < 0.05$ for each comparison) in areas shown in pink. Areas shown in light blue show higher correlations for the opaque orthographies compared with the transparent orthography, $P < 0.05$. (B) Scatter plots of the correlation between print and speech activation in representative areas showing greater convergence for more transparent languages in left inferior parietal lobe, supramarginal gyrus (left), and left angular gyrus for opaque languages (right).

Source: Adapted with permission from Rueckl et al. (2015).

has been provided by studies using diffusion-weighted imaging (DWI; see Catani & Forkel, Chapter 9 in this volume). This technique allows the identification of white matter micro-structure properties of the fiber bundles connecting distant cortical regions. Structural connections between temporal and frontal cortical regions are mediated by different ventral and dorsal fiber tracts (Friederici, 2012; Saur et al., 2008). For instance, using a deterministic fiber-tracking approach with the two end points of the connections predefined on the basis of functional data, Saur et al. (2008) showed that within the ventral pathway, the extreme fiber capsule system (connecting temporal cortex with *pars triangularis* and *pars orbitalis*) supported sound-to-meaning mapping. On the other hand, the structural dorsal pathway (going from the temporal lobe to the premotor cortex and continuing to the *pars opercularis*, via the arcuate and superior longitudinal fascicle) supported sensorimotor mapping of sound-to-articulation.

READING IN BILINGUALS

A relevant demand in today's world is the need to speak more than one language. The rapid need for bilingualism and multilingualism in modern societies encourages a significant proportion of individuals to learn new languages over childhood and adult years. How does the brain accomplish such a feat? How is language organized in individuals who know more than one language? The following section provides a description of the neural mechanisms underlying bilingual reading.

Bilingualism is increasingly common in most of the world today. In many countries, bilingualism is the norm, while in predominantly monolingual countries (e.g., the United States) the size of the bilingual population has been steadily growing over the last two decades. Thus, it is not surprising that study of the neural correlates underlying bilingualism is also on the increase. For people who speak two languages, understanding tens of thousands of words in each language is an exceptional accomplishment of their cognitive and neural systems. One of the main issues in this area that is generating heated debate is to what extent bilinguals share or do not share the same neural networks for their L1 and L2 (Parker Jones et al., 2012; Price, 2012; Schlaggar & McCandliss, 2007). Neuropsychological evidence has shown that injuries to Broca's area in bilinguals can produce deficits in language production (i.e., expressive aphasia) in their L1, but not necessarily in their L2 (Wolf et al., 1999). In contrast, neuroimaging research has yielded mixed results in this regard, with some studies revealing differential regional activation in L1 relative to L2 processing (Kim, Relkin, Lee, & Hirsch, 1997) and other studies showing extensive overlap among the regions recruited for L1 and L2 processing (Friederici, Steinhauer, & Pfeifer, 2002; Musso et al., 2003).

Nevertheless, there are some relevant factors that are known to influence the functional and structural correlates of reading networks in bilinguals, such as the age of acquisition (AoA) of the L2, the proficiency level, exposure, and language orthography (Jamal et al., 2012; Mechelli et al., 2004; Perani et al., 2003; Wartenburger et al., 2003). These factors can explain these and other inconsistencies in neuroimaging research in regard to the overlap or the lack of overlap between L1 and L2 regions and networks involved in bilingual reading. A description of the functional and structural findings regarding these factors is discussed next.

Age of Acquisition

The fact that children appear to acquire an L2 faster and more efficiently than adults suggests the existence of a temporal window for optimal L2 learning (see Lennenberg, 1967, for the concept of critical period). Evidence supporting the existence of an optimal temporal window for L2 learning is supported by neuropsychological studies of bilinguals with different L2 AoA. Findings from these studies have revealed that language recovery in aphasics is considered to be excellent if occurring in early infancy, while older children show more adult-like aphasic patterns and poorer recovery (Bates et al., 2001; see Reilly & Polse, Chapter 10 in this volume). While neuroimaging studies of bilingual reading are still relatively scarce, extensive overlap in perisylvian regions for L1 and L2 reading has been typically found in early bilinguals, but not in late bilinguals (Kim et al., 1997; Wartenburger et al., 2003). In particular, Kim et al.'s (1997) study revealed that separate but adjacent tissue of Broca′s area (encompassing IFG *pars opercularis* and *triangularis*) was activated for L1 and L2 in late bilinguals, whereas stronger overlap within this region was found in early bilinguals for L1 and L2 processing. More recently, similar results were observed in reading studies with bilinguals (Wartenburger et al., 2003), and also in studies focused on different language-related processing, such as syntax (Mahendra, Plante, Magloire, Milman, & Trouard, 2003) and lexical aspects (Isel & Shen, 2011) This evidence indicates that the later an L2 is acquired, the less the overlap observed in cortical representations for L1 and L2. This means that additional resources are required in late bilingual L2 processing to achieve native-like performance. In contrast, early bilinguals learn both languages in parallel and appear to show stronger overlap in brain regions for processing L1 and L2 (Hernandez & Li, 2007; Perani & Abutalebi, 2005).

The effects of L2 AoA have been also investigated using structural measures. Empirical evidence suggests that the earlier bilinguals begin L2 learning, the more gray-matter density is found in the left inferior parietal cortex (Mechelli et al., 2004). The structural changes in this region are described as reflecting explicit learning strategy for linking new words to concepts (Richardson, Seghier, Leff, Thomas, & Price, 2011), a process that is implicit when learning languages from birth. Furthermore, differences in white-matter microstructure also have been found as a function of the AoA. Early bilinguals relative to late bilinguals exhibited higher fractional anisotropy (FA; a measure of the coherence of directionality of white-matter fibers) values in the left inferior frontal occipital fasciculus (IFOF), which has been suggested to play a role in semantic processing (Mohades et al., 2012). Higher FA values may be related to increased structural connectivity between reading related regions, such as among the regions that the IFOF connects, due to greater language experience or automaticity (Mohades et al., 2012; Schlegel, Rudelson, & Peter, 2012). Recently, one study suggested that later acquisition of L2 is associated with thicker cortex in the left IFG, a crucial region within the reading network (Klein, Mok, Chen, & Watkins, 2014), interpreted by the authors to be due to less synaptic pruning in this region as a result of acquiring L2 later in development. Overall, the bulk of evidence suggests that acquiring an L2 as a new skill earlier or later in life induces different functional and anatomical changes in reading- and language-related regions.

Language Proficiency

Some studies have pointed to proficiency as the main factor determining differences in the recruitment of neural regions for reading in L1 and L2. Neuroimaging studies have shown that lower proficiency in the L2 is associated with greater IFG *pars orbitalis* activation during reading (Chee, Hon, Lee, & Soon, 2001). Convergent evidence showing hyperactivation in participants with lower versus high proficiency was found in studies examining other language-related tasks, such as verbal fluency (Vingerhoets, 2003), semantic and syntactic judgments (Wartenburger et al., 2003), and naming tasks (Hernandez, Dapretto, Mazziotta, & Bookheimer, 2001). This hyperactivation during L2 reading and other L2 language-related processes may be due to a lower degree of automaticity because of the lower proficiency in L2. In line with this interpretation, when L2 and L1 proficiency are equated, early and late bilinguals tend to exhibit strikingly similar neural responses for processing both the L1 and L2 (Abutalebi, Cappa, & Perani, 2001; Chee et al., 2001; Frenck-Mestre, Anton, Roth, Vaid, & Viallet, 2005; Klein, Watkins, Zatorre, & Milner, 2006). Thus, as L2 proficiency increases, differences in the neural correlates of reading in L1 versus L2 decrease. AoA effects might therefore be diminished when early and late learners are equated on proficiency.

Furthermore, L2 proficiency also seems to induce changes in structural measures. L2 proficiency correlates with increased gray-matter density in a variety of reading-related regions, such as left inferior parietal cortex (IPC) (Mechelli et al., 2004), left IFG (Grogan, Green, Ali, Crinion, & Price, 2009; Stein et al., 2012) and left STG (Martensson et al., 2012). Additionally, increases in WM connectivity between left-hemispheric perisylvian regions and their right homolog regions (IFG, caudate nucleus, STG) are related to the level of L2 proficiency in English learners of Chinese (Schlegel et al., 2012). In sum, higher L2 proficiency is associated with increased gray-matter density or structural increases in gray matter and also with increased white-matter connectivity in reading-related fiber tracts.

Language Exposure

The level of exposure to L1 and L2 has also been implicated in modulation of the neural correlates of reading processes in bilinguals (e.g., Tu et al., 2015). Even when the degree of proficiency is kept constant, differential exposure seems to be associated with differential engagement of reading-related regions (Vingerhoets et al., 2013). Similar results have been observed in studies using language-related tasks other than reading. For example, Perani et al.'s (2003) study compared two groups of highly proficient bilinguals, differing in their L2 exposure, on a word-generation task. Participants with high L2 exposure exhibited reduced activation in left prefrontal cortex relative to those with lower L2 exposure. Thus, experience and practice in the L2 may result in a decrease of neural activation, suggesting more automaticity and less effort or resources needed for L2 processing (Abutalebi, 2008; see Green & Kroll, Chapter 11 in this volume). Recent evidence also suggests that even brief 30-day periods of differential exposure to a given language may induce significant neural changes in areas responsible for language processing (Tu et al., 2015). Furthermore, neuroimaging studies have proposed that L2 exposure can even replace L1 when bilinguals are no longer exposed to their native language (Pallier et al., 2003). The role of L2 exposure was also investigated in a few structural studies that found correlations between L2 exposure and gray-matter density in language-related regions, such as the bilateral posterior putamen (Pliatsikas, Johnstone, & Marinis, 2014). Based on these neuroimaging findings, the amount of language exposure seems to affect the functional and structural neural responses involved in L2 processing.

Language Orthography

Orthographies vary across languages in their grapheme-to-phoneme correspondence. Orthography differences modulate the involvement of the functional reading networks (Paulesu et al., 2000; Rueckl et al., 2015). Disparities in the activation of reading networks may be also visible in bilinguals with two different language orthographies (e.g., Spanish-English bilinguals). In fact, Meschyan and Hernandez (2006) reported differences in activation profiles for early Spanish-English bilinguals during L1 and L2 reading. More specifically, in Meschyan and Hernandez's (2006) study, Spanish reading elicited greater activation in the right supplementary motor area, right putamen, right insula, and left STG. In contrast, English reading elicited greater activation in the IPC and along regions in the occipito-parietal vicinity. However, participants in this study differed in proficiency, and so it is not clear if these differences were due to proficiency or to language orthography per se. A more recent study of Spanish-English late bilinguals matched in proficiency revealed functional differences in the reading network as a function of language orthography (Jamal et al., 2012). Interestingly, one study that tested simultaneous and sequential Hindi-English bilinguals showed a division of labor with more ventral activation for English (an opaque orthography) and more dorsal activation for Hindi (a transparent orthography), as is the case for each language in English and Hindi monolinguals. However, sequential bilinguals with late exposure to English showed more dorsal activation when reading both in English and in Hindi (Das, Padakannaya, Pugh, & Singh, 2011). The findings of this study suggest that early, but not late, exposure to reading distinct orthographies results in orthography-specific plasticity that persists through adulthood. Altogether, this evidence suggests that bilinguals show changes to the typical neural representations of reading, depending upon language orthography. However, it is still not clear what specific neural representations are expected as a function of the orthography and if this divergent activation is confounded with other variables, such as AoA.

Importantly, a recent study (Oliver et al., 2017) examining the functional dynamics of ventral and dorsal reading networks in bilinguals with the same L1 (i.e., Spanish) and either an opaque (i.e., English) or transparent (i.e., Basque) L2 showed that differences in orthographic depth of the L2 were associated with strikingly segregated profiles in the coupling of left vOT with regions along the ventral network in the group with an opaque L2, on the one hand, and with regions along the dorsal network for the group with a transparent L2, on the other (Figure 24.4). These results were observed during word reading, with further analysis indicating that this pattern of co-activation with left vOT holds for word reading in L2, but not for word reading in L1. Oliver et al.'s (2017) findings

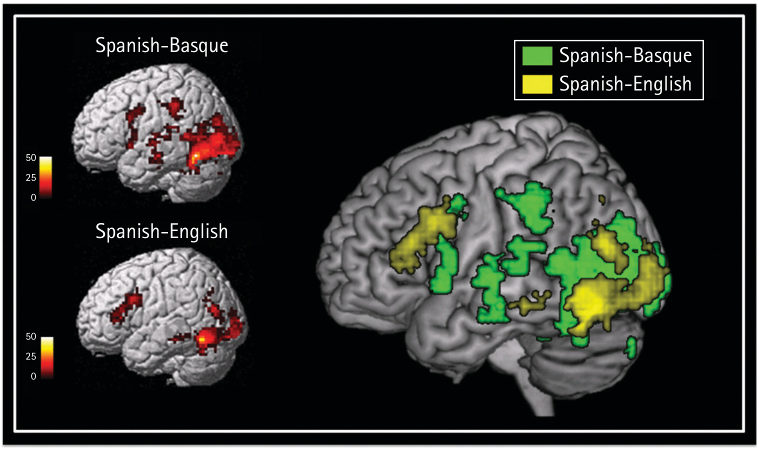

FIGURE 24.4. Left-hemisphere brain renderings showing whole-brain functional connectivity maps with left vOT for the contrast Words > Null separately for the Spanish-Basque (in green) and Spanish-English (in yellow) groups at a voxel-wise FDR-corrected statistical threshold of $q < .0001$.

Source: Modified with permission from Oliver et al. (2017).

are consistent with evidence suggesting that transparent orthographies with strong letter-to-sound mapping rely more on dorsal regions and that opaque orthographies rely more on lexico-semantic processes carried out by regions along the ventral pathway (Das et al. 2011; Paulesu et al., 2000; Rueckl et al., 2015).

In sum, based on the research evidence reviewed in this section, it is possible to conclude that the brain has an extraordinary ability to functionally and structurally change in response to environmental stimuli, cognitive demands, and experiences. Specifically, reading demands, type of stimuli, AoA, language proficiency and exposure, and language orthography are crucial factors that can affect the brain representations of each language in bilingual reading. Despite recent advances in cognitive neuroscience regarding bilingual reading, results from functional and structural studies with bilingual populations are still scarce and inconsistent. Future studies should take into account the influence of the variables reviewed here (i.e., AoA, proficiency, exposure, language orthography) and the importance of controlling or manipulating these within the same study. Importantly, there is also increasing evidence that individual differences in functional activation are related to underlying brain structure. Therefore, future investigations can shed further light on the neural bases of bilingual reading by combining structural and functional data in the same study.

CONCLUSIONS

Neuroimaging research on the neurobiology of reading has provided critical insights about how monolingual and bilingual brains achieve reading. In the present chapter, we have reviewed well-established findings and current debates on the (1) functional specialization of left perisylvian reading regions and their participation in orthographic, phonological, and sematic reading systems; (2) the division of labor between ventral and dorsal reading networks and the factors that modulate them; and (3) the neural correlates supporting bilingual reading and the impact of AoA, language proficiency, language exposure, and language orthography in the modulation of bilingual reading regions and networks. Additional research is still needed to further inform ongoing debates, particularly with regard to the factors that modulate bilingual reading. This area is of growing theoretical and practical interest due to the fact that more than half of the world's population is bilingual, but little is still known about what the most beneficial and efficient educational practices are for reading acquisition in bilingual and multilingual populations.

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CHAPTER 25

DYSLEXIA AND ITS NEUROBIOLOGICAL BASIS

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INTRODUCTION

DEVELOPMENTAL dyslexia (DD) is one of the most prevalent developmental learning disabilities, affecting approximately 7%–10% of school-age children (Lyon, Shaywitz, & Shaywitz, 2003). Extensive research in the areas of education, psychology, linguistics, and cognitive science conducted in the past several decades has identified a core set of reading behaviors that are characteristic of children with DD, including poor decoding and spelling, despite typical levels of intelligence. Although DD is a complex, polygenetic disorder it is widely accepted that many children with dyslexia have a primary impairment in phonological processing (Harm & Seidenberg, 1999; Katz, 1986; Kovelman et al., 2012; Tanaka et al., 2011; Vellutino, Pruzek, Steger, & Meshoulam, 1973; Wagner & Torgesen, 1987; Ziegler, Perry, Ma-Wyatt, Ladner, & Schulte-Korne, 2003). This hypothesis is supported by consistent findings that early deficits in phonological awareness predict poor reading ability (Foy & Mann, 2006; Goswami & Bryant, 1990; Hulme, 2002; Hulme, Caravolas, Málkova, & Brigstocke, 2005; Penke & Schrader, 2008; Scarborough, 1990; Snowling, 1987; Snowling, Van Wagtendonk, & Stafford, 1988; Stanovich, 1988; Wagner & Torgesen, 1987). However, an observed deficit in phonological processing could be caused by one or more underlying factors, including deficits in sensory processing (Stein & Walsh, 1997; Tallal, 2004); visual attention (Bosse, Tainturier, & Valdois, 2007); sensitivity to amplitude rise times or temporal processing (Goswami et al., 2002); access to phonological representations (Boets, 2014; Boets et al., 2013); or sensorimotor integration (Kuhl, 2004; Preston et al., 2010; Pugh et al., 2013).

Although phonological deficits are typically observed in DD, some children with phonological deficits do not have dyslexia, and the severity of phonological deficits alone does not predict the severity of dyslexia (Peterson, Pennington, Shriberg, & Boada, 2009; Snowling, 2000; Valdois et al., 2011). Given the considerable heterogeneity associated with DD and the complex profile of deficits observed across children with DD, it is becoming increasingly clear that dyslexia is unlikely to be reduced to one casual mechanism (Pennington, 2006; van Bergen, van der Leij, & de Jong, 2014; Wolf & Bowers, 1999). The *multiple deficit model* put forth by Pennington (2006) and elaborated by van Bergen and colleagues (2014) proposes that multiple genetic factors act probabilistically, in combination with environmental factors, to produce a continuum of liability for dyslexia and other developmental disorders. This model has particular power for explaining the high comorbidity observed between DD and other neurodevelopmental disorders, including specific language impairment (SLI)/ Developmental Language Disorder (DLD), attention-deficit hyperactivity disorder (ADHD), dyscalculia, and speech-sound disorder. Elevated incidence of one of these disorders given the presence of another suggests that they are not etiologically independent. Neurobiological evidence, including both neuroimaging and genetic studies of DD, can inform theories of reading that seek to better understand both the observed heterogeneity in DD and the high rate of comorbidity between DD and other developmental disorders (see Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24 in this volume). The following sections review profiles of perceptual and cognitive performance associated with dyslexia, as well as its genetic and neurobiological bases, including recent contributions from imaging genetic approaches.

PHONOLOGICAL DEFICIT HYPOTHESIS

The *phonological deficit hypothesis* assumes that the underlying cause of dyslexia is primarily a deficit in representation of phonological information, access to phonological information, or manipulation of phonological information. This hypothesis has been widely supported because the primary impairments observed in dyslexia involve phonology, including poor phonological awareness, poor phonological memory, and poor grapheme to phoneme mapping (Joanisse et al., 2000; Snowling, 2000). The pivotal place of phonological processing deficits in dyslexia has been further supported by results from neuroimaging studies that highlighted the central role of phonological activation in fluent word reading (see Pugh et al., 2000; Norton et al., 2015; Sandak, Mencl, Frost, & Pugh, 2004).

Phonological awareness (PA), a meta-phonological skill that requires both the awareness of individual speech sounds that make up words and the ability to manipulate them, has been identified as a particularly strong predictor of reading skill (Foy & Mann, 2006; Goswami & Bryant, 1990; Hulme, 2002; Hulme et al., 2005; Wagner & Torgesen, 1987). Children with better phonological awareness perform better on tasks such as indicating the number of syllables or phonemes in a word, naming a word that differs from other words in onset, rime, or vowel (such as *toy, boy, bay*), repeating a word while omitting a phoneme, or matching words that contain the same sound, and they are more likely to become better readers. The strong relationship between PA and reading is linked that children's underlying understanding that individual speech sounds map onto letters, and the proper representation of these mappings underlie successful decoding of new words (Share, 1995; Share & Gur, 1999).

The ability to store phonological codes in short-term memory (phonological loop) and maintain information about words and their meanings as lexical access occurs is also necessary for skilled reading (Alloway, Gathercole, Willis, & Adams, 2004; Chein & Schneider, 2005). Phonological short-term memory, which involves preserving new incoming information while simultaneously being able to process this information and integrate it with existing information (Baddeley, 1987), is also predictive of reading decoding and fluency (McCallum et al., 2006). Further, children with poor short-term working memory capacity, particularly in the verbal storage system, are more likely to be poor readers (Gathercole, Tiffany, Briscoe, & Thorn, 2005; Swanson & Jerman, 2007).

Impaired phonological representations may arise from speech perception problems that compromise phonological representations, which manifest as higher-order phonological processing and reading impairments. Phonological representations in dyslexia may be underspecified (e.g., Elbro, Nielsen, & Petersen, 1994), causing confusion between similar speech sounds, and in turn, phonological processing difficulties. Indeed, several studies find support for impaired phonological representations that correspond to higher-level phonological processing, including impaired categorical perception (Godfrey, Syrdal-Lasky, Millay, & Knox, 1981; Messaoud-Galusi, Hazan, & Rosen, 2011), and others have revealed significant associations between early production delays and reading difficulties (Preston et al., 2010).

Alternatively, some have suggested that children with dyslexia may have overspecified representations at the allophonic (sub-phonemic variations within phoneme categories) level rather than phonemic level of representation, which may be problematic for acquiring stable mappings between phonemes and graphemes (Bogliotti, Serniclaes, Messaoud-Galusi, & Sprenger-Charolles, 2008; Serniclaes, Collet, & Sprenger-Charolles, 2015; Serniclaes, Van Heghe, Mousty, Carre, & Sprenger-Charolles, 2004). Indeed, individuals with dyslexia have been shown to discriminate between within-category allophonic variants of the same phoneme, whereas non-dyslexic readers perceive allophonic variants as the same phoneme (Serniclaes, Van Heghe, Mousty, Carre, & Sprenger-Charolles, 2004). Moreover, behavioral studies of Dutch children at risk for dyslexia showed that these children demonstrate a shift during kindergarten from allophonic perception to phonemic perception in first grade, whereas non-dyslexic children already demonstrate developed phonemic perception in kindergarten (Noordenbos, Segers, Serniclaes, Mitterer, & Verhoeven, 2012a). Further, mismatch negativity response (MMN, an electrophysiological measure of discrimination; see Leckey & Federmeier, Chapter 3 in this volume) to both phonemic and allophonic contrasts have been observed in adults with dyslexia, but only for phonemic contrasts in adults without dyslexia (Noordenbos, Segers, Serniclaes, Mitterer, & Verhoeven, 2012b). Finally, yet another possibility is that access to phonological information, rather than representation per se, may be the source of the phonological deficit in dyslexia, discussed further under neurobiological bases (Boets, 2014; Boets et al., 2013).

DOUBLE-DEFICIT HYPOTHESIS

Impairments in the processes that underlie rapid word recognition have been detected in children with dyslexia, and have been shown to be at least partially independent of impairments in phonology, indicating that other aspects of language and cognition contribute to the development of reading. As mentioned earlier, not all children with poor phonological processing skills (broadly construed) will have reading difficulty (Snowling, 2008), and not all children with reading difficulty necessarily show poor phonological skills (Pennington et al., 2012; Valdois et al., 2011; van Bergen et al., 2014). Thus, impairments in phonological processing may represent only a portion of the deficit in dyslexia, and deficits in processing speed have been hypothesized to contribute to dyslexia profiles as well. Wolf and Bowers (1999) offered a *double-deficit hypothesis* for reading impairment that implicated both phonological and speed of naming processes as separate sources of reading difficulty (Katzir, Kim, Wolf, Morris, & Lovett, 2008; Wolf, Bowers, & Biddle, 2000). Children with DD often present with a discrete deficit in either phonological processing or processing speed, or a combination of both (McCardle, Scarborough, & Catts, 2001). However, naming speed is not completely independent from phonological processing, given that a word's phonological form is accessed while reading.

A key finding supporting the double deficit hypothesis is that children's performance on the Rapid Automatized Naming (RAN) task has been shown to be predictive of fluent word reading (Wolf & Bowers, 1999). Typical RAN tasks involve speeded naming of familiar stimuli (e.g., digits, letters, colors), and poor performance on this task is associated with dyslexia (Bowers & Swanson, 1991; Denckla & Rudel, 1974). Importantly, RAN makes independent contributions to reading ability (Bowers & Swanson, 1991; Wolf et al., 2002). That is, when phonological awareness ability has been accounted for, RAN scores still significantly predict reading (Wolf et al., 2002). Speed of processing during lexical access and the accurate retrieval of information that underlie RAN are also components of multiple other cognitive abilities, and successful RAN performance depends on other cognitive processes and abilities as well (e.g., attention; Arnell, Joanisse, Klein, Busseri, & Tannock, 2009). For example, children with ADHD show poorer performance on RAN measures than typically developing children (Waber, Wolff, Forbes, & Weiler, 2000), as good performance on RAN tasks requires sustained attention and the ability to exhibit inhibition of previous and upcoming responses while the current response is executed (Wolf & Bowers, 1999). Thus RAN impairments suggest deficits in the ability to process information accurately and quickly that go beyond phonological processing. In the following, we review other processing deficits that are hypothesized to contribute to dyslexia.

SENSORY-PROCESSING DEFICITS

As described earlier, phonological processing is a critical component of reading. Importantly, the development of robust phonological representations depends on intact sensory processing involved in auditory learning that is supported by multisensory information, including motor information from producing speech and visual information from the face (Kuhl, 2004). Following on this argument, several theoretical approaches have put forth low-level visual- and auditory-processing deficits as having a possible causal role in the development and manifestation of dyslexia.

The *magnocellular theory* posits deficits in the dorsal visual pathway (Stein & Walsh, 1997) as a causal mechanism for dyslexia. For example, deficits have been observed in the ability of children with dyslexia to effectively parse the visual field (detect motion, process spatial position)—the domain of magnocellular visual processing (Stein & Walsh, 1997), However, other research suggests that visual processing that depends on the magnocellular system is intact in individuals with dyslexia, or that deficits are only observed when information is presented in noisy conditions (i.e., under increased cognitive and attentional load). Sperling, Lu, Manis, and Seidenberg (2005) found that individuals with dyslexia perform more poorly than individuals without dyslexia when identifying visual patterns presented in noisy conditions (akin to television static). However, individuals with and without dyslexia perform alike when identifying visual patterns presented in non-noisy conditions, suggesting that the deficit lies in signal-noise discrimination rather than magnocellular processing (Sperling et al., 2005). Moreover, compelling data suggest that the magnocellular visual-processing impairments may not be a cause of dyslexia, but rather a consequence of limited reading experience itself (Amitay, Ben-Yehudah, Banai, & Ahissar, 2002; Olulade, Napoliello, & Eden, 2013). Specifically, in one functional magnetic resonance imaging (fMRI) study, Olulade and colleagues (2013) found reduced neural activation in the V5/MT brain regions that support magnocellular visual processing in children with dyslexia, compared to children without dyslexia; however, no differences in neural activation in V5/MT were observed between children with dyslexia and younger children matched for reading ability. Additionally, when children with dyslexia took part in a phonologically based reading intervention, activation in the V5/MT region also increased, suggesting a causal relationship between reading experience and magnocellular visual processing (Olulade et al., 2013).

Impaired visual attention (the amount of information that can be maintained with interrupted input, such as blink or saccades) and impaired visuospatial attention (the ability to orient spatial attention) can also limit reading ability (Bosse et al., 2007; Facoetti et al., 2003). Indeed, individuals with dyslexia show longer (i.e., slower) response times to visual and auditory stimuli in cued-detection task (whereby a cue directs attention toward a response), indicating slower attentional processing (Facoetti et al., 2010). Further, differences in the time course of attentional processing accounts for variance in children's nonword reading performance above and beyond the contribution of phonological ability (Facoetti et al., 2010); note, however, that children with dyslexia in this study also had poor pre-reading phonological awareness. Children with dyslexia also showed gains in spatial attention, phonological recoding, and reading speed after receiving active video-game training intervention (Franceschini et al., 2013). One notable difficulty with studies of visual attention in dyslexia is that their designs limit the ability to infer causal relations (e.g., to date there are no studies including children with dyslexia as well as younger reading-matched controls); as such, like deficits in magnocellular visual processing, the deficits observed in visual attention may be the product of reduced reading experience, which could train up visual attention, rather than a causal mechanism of dyslexia (Facoetti et al., 2003; 2006).

In addition to visual processing and visual/visuospatial attention-deficit hypotheses, impaired *auditory processing hypotheses* postulate a causal connection between auditory dysfunction and phonological deficits, frequently observed in individuals with dyslexia. Thus, the inability to perceptually organize the auditory input that makes up speech can manifest in impaired phonological processing ability. The rapid auditory processing (RAP) deficit hypothesis proposes that a specific deficit in the ability to process rapidly and sequentially presented auditory information causes dyslexia (Tallal, 2004). The premise of the hypothesis lies in the fact that spectral changes that are relevant for speech (e.g., frequency variation in transitions from consonants to vowels) are quite rapid (around 40 ms). Children with language impairment show poorer ability to process rapid auditory information; this deficit was suggested to also account for the phonological deficits observed in children with dyslexia (Tallal, 1980, 2004). However, empirical evidence with respect to this hypothesis has been mixed: only some children with dyslexia show this processing difficulty (Beaton & Davies, 2007; Boyer & Ehri, 2011; Goswami, Gerson, & Astruc, 2010); thus, the deficit might have a more prominent role in SLI than dyslexia. Moreover, if processing *rapid* temporal information of speech is the critical deficit in poor phonological performance in children with dyslexia, then slowing down the temporal information should improve phonological performance in this group; however, that is not the case (McAnally, Hansen, Cornelissen, & Stein, 1997).

Another sensory-based theory put forth by Goswami and colleagues (2002), the *rise time theory*, instead focuses on slower auditory processing and/or impaired discrimination of amplitude (or intensity) in speech in children with dyslexia. According to this account, the deficits observed in dyslexia might stem from impairments in discriminating rise time, a measure of the rate of change in amplitude at the onset of a speech segment, which affects the detection of speech rhythms that correspond to prosodic and syllabic processing rates. Evidence for this theory comes from findings of impaired rise time discrimination at slow temporal rates in children with dyslexia compared to age-matched typically developing readers and reading-matched younger readers across multiple languages and orthographies (Goswami, Fosker, Huss, Mead, & Szucs, 2011; Poelmans et al., 2011). Moreover, children and adults with dyslexia have been shown to exhibit prosodic deficits or reduced prosodic awareness (Goswami, Huss, Mead, Fosker, & Verney, 2013; Kitzen, 2001), and children with dyslexia are poorer than age-matched controls and younger reading age-matched controls at judging musical rhythm with similar rise times (Goswami et al., 2013). Finally, at the neural level (see also the following discussion of the neural basis of dyslexia), children with dyslexia show atypical neural entrainment (captured by EEG phase alignment) to syllable streams at 2 Hz (Power, Mead, Barnes, & Goswami, 2013).

Neural Basis of Dyslexia

Neuroimaging studies of dyslexia have been instrumental in informing our knowledge of the biological bases of dyslexia. What has emerged from findings using fMRI (see Heim & Specht, Chapter 4 in this volume) and positron emission tomography (PET) is that children and adults with dyslexia have atypical functional brain activation (during reading and reading related tasks) in a network of left hemisphere language regions (Landi et al., 2010; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Paulesu et al., 2001; Price & Devlin, 2011; Pugh et al., 2001; Richlan, Kronbichler, & Wimmer, 2009, 2012; Rumsey et al., 1997; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Shaywitz et al., 2002; Temple et al., 2003). This atypical activation most commonly manifests as hypoactivation in several regions, including left temporo-parietal (superior temporal gyrus [STG], angular gyrus [AG], inferior parietal lobe [IPL]), occipito-temporal gyrus (OT), and inferior frontal gyrus (IFG), during reading. In some studies, individuals with dyslexia also showed compensatory right hemisphere activity and/or increased left IFG or other frontal lobe activation; however, some evidence suggests that these differences may be age-dependent, and thus a byproduct of reading skill (Sarkari et al., 2002; Shaywitz et al., 1998; Shaywitz et al., 2000; Shaywitz et al., 2002; Simos et al., 2002). In addition to reduced activation, several reports indicate reduced functional connectivity between a number of the aforementioned left hemisphere regions during reading tasks (e.g., Hampson, Olson, Leung, Skudlarski, & Gore, 2004; Pugh et al., 2000). Recent findings further suggest that the degree to which individuals use the same left hemisphere regions (including STG, IFG, and inferior parietal cortex) for both print and speech processing is associated with reading skill, and is predictive of later reading success in young readers (Frost et al., 2009; Preston et al., 2016). Although this research did not include a large number of clinically defined readers with dyslexia, continuous approaches to examining brain-behavior relations have successfully replicated group comparisons (e.g., Pugh et al., 2013; 2014). Other recent findings highlight a potential role for subcortical structures, including the basal ganglia and thalamus, in reading and reading disorder, suggesting a possible link to some of the observed procedural learning deficits observed in dyslexia (Preston et al., 2010; Pugh et al., 2013).

In addition to these functional neuroimaging differences, structural differences have also been observed in the form of smaller gray matter volume in a number of the left hemisphere regions that show functional differences in individuals with dyslexia (e.g., Brambati et al., 2004; Kronbichler et al., 2008). Further, atypical white matter integrity has also been observed in tracts that connect these same language and reading critical regions (Boets et al., 2013; Niogi & McCandliss 2006; Vandermosten, Boets, Wouters, & Ghesquière, 2012).

In order to disentangle cause and consequence of dyslexia, researchers have begun to explore neural circuitry in pre-reading children and infants at increased familial risk for dyslexia. Taking this approach, Raschle, Chang, and Gaab (2011) found reduced gray matter volume (GMV) in temporo-parietal and occipito-temporal regions in at-risk pre-reading children relative to controls who were not at risk; further, GMV was correlated with RAN in these regions, and phonological processing was correlated with a region in the left occipito-temporal cortex (Raschle et al., 2011). At the level of function, at-risk, pre-reading children showed hypoactivation during a phonological-awareness task in key left hemisphere reading-associated regions, including the left lingual gyrus, left STG/MTG, and this activation also correlated with performance in a PA task (Raschle, Zuk, & Gaab, 2012). Further, at-risk pre-reading children also showed positive correlations between their phonological awareness ability and both the volume and fractional anisotropy (FA) of the left arcuate fasciculus, a prominent white matter fiber tract (Saygin et al., 2013; see Catani & Forkel, Chapter 9 in this volume).

Recent evidence from electroencephalography (EEG) and event-related potential (ERP) research (see Leckey & Federmeier, Chapter 3 in this volume) has also contributed to the neurobiological profile of dyslexia. Differences in the MMN component to speech tokens have been found between infants with and without family risk who go on to have dyslexia (Leppanen et al., 2012; Molfese, 2000; Van Zuijen, Plakas, Maassen, Maurits, & van der Leij, 2013), and between young children who have dyslexia and their siblings who are at heightened genetic risk but do not have dyslexia (Neuhoff et al., 2012). Further, there is evidence that, unlike controls, individuals with dyslexia do not show inter-trial delta phase (2 Hz) coherence (the temporal rate with which stressed syllables occur in speech), and that individuals with dyslexia show reduced expectancy-based response (contingent negative variation, CNV) to these rhythms (Hamalainen, Rupp, Soltesz, Szucs, & Goswami, 2012; Soltész, Szűcs, Leong, White, & Goswami, 2013). Individuals with dyslexia, unlike controls, also do not show left dominant auditory entrainment to phoneme level (25–35 Hz) modulation in auditory cortex, and present with bilateral abnormal responses at a higher rate (>50 Hz), which could indicate that they have finer grained phonemic representations than controls (Lehongre, Ramus, Villiermet, Schwartz, & Giraud, 2011); that is, as discussed earlier in the chapter, individuals with dyslexia may represent subphonemes, which could present as an impairment in phonological awareness and memory if they are holding on to and manipulating more information than required (e.g., Dufor, Serniclaes, Sprenger-Charolles, & Demonet, 2009).

In contrast to these auditory EEG and ERP findings, recent fMRI findings suggest the possibility that phonological representations in individuals with dyslexia in the temporal cortex are in fact intact, but that access to them may be impaired (Boets, 2014; Boets et al., 2013). Specifically, Boets and colleagues (2013) examined patterns of neural activation between adults with and without dyslexia while discriminating vowels and stop-consonants. Both dyslexic and nondyslexic adult readers showed distinct neural activation patterns for all speech sounds that differentially rely on spectral and spectrotemporal acoustic feature processing, suggesting robust phonetic representations. However, the functional and structural connectivity between auditory cortices and the left IFG was reduced in individuals with dyslexia, but not in individuals without dyslexia, suggesting that poor access to otherwise intact phonological representations is the core feature of the phonological deficit in dyslexia. Additional support for this hypothesis comes from several studies mentioned previously that have documented abnormalities in the arcuate fasciculus in older individuals with dyslexia and in pre-reading children with low PA (Saygin et al., 2013; Vandermosten, Wouters, & Ghesquière, 2014).

Genetic and Imaging Genetic Approaches

Twin and family studies have established the high heritability of reading ability and reading problems; depending on variables such as socioeconomic status (SES), age, gender, and IQ, genetic effects account for 40%–80% of the variance in different reading and reading-related skills (Byrne et al., 2009; Grigorenko, 2004; Taylor, Roehrig, Soden Hensler, Connor, & Schatschneider, 2010). With respect to molecular genetic studies of dyslexia, nine candidate dyslexia genetic loci, which have been labeled DYX1–DYX9, have been proposed. Fine-mapping of these regions has identified several candidate genes that play a role in neuronal migration or axon guidance during development, including *DYX1C1* (Taipale et al., 2003), *DCDC2* (Meng et al., 2005), *KIAA0319* (Cope et al., 2005), and *ROBO1* (Hannula-Jouppi et al., 2005). In addition to their association with dyslexia, these genes have been associated with behaviors and endophenotypes related to dyslexia; for example, *DYX1C1* has been associated with deficits in memory, phonological decoding, sight word reading, orthographic decoding, RAN, and spelling (Bates et al., 2010; Dahdouh et al., 2009; Marino et al., 2007; Taipale et al., 2003); *KIAA0319* and *DCDC2* have been associated with phonological awareness, spelling, phonemic decoding, and sight word reading (Eicher et al., 2015; Francks et al., 2004; Kaplan et al., 2002.; Meng et al., 2005; Scerri et al., 2011; Turic et al., 2003); and, *ROBO1* has been associated with phonological memory, word reading, and spelling (Bates et al., 2011; Tran et al., 2014).

Given that complex neurodevelopmental disorders that are heterogeneous with compound phenotypes are likely to be regulated by multiple genes and gene-gene as well as gene-environment interactions, recent studies have taken a network or path approach to studying dyslexia and other complex disorders (e.g., Biernacka, Jenkins, Wang, Moyer, & Fridley, 2012). These approaches move away from focusing on the primary association between phenotype and single nucleotide polymorphisms (SNPs) individually to include path-level analyses and/or analyses that specifically look for gene-gene or gene-environment interactions based on hypothesized relationships (Winham & Biernacka, 2013). One study that has utilized this approach to study dyslexia risk found that patterns of combined genotypes across multiple SNPs on *KIAA0319* (i.e., haplotypes) conferred specific levels of risk for dyslexia (Shao et al., 2016). A second example comes from a recent study that found gene-gene interactions between multiple markers in *DYX1C1, KIAA0319,* and *GRIN2B*—genes associated with worse performance on memory for letters in a sample of families with dyslexia (Mascheretti, Bureau, Trezzi, Giorda, & Marino, 2015).

Another approach that yields promise for understanding the mechanisms by which genes lead to behavioral change includes neuro-endophenotypes measured with MRI or EEG/ERP or MEG (see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume). This approach builds on prior knowledge from early behavioral neuroscience approaches that identified abnormal neuronal migration and ectopias in the temporal lobes of rodents whose genome had been modified to knock out (or knock down) a dyslexia candidate gene; similar abnormalities in neuronal migration were also identified in post mortem studies of several individuals with a history of dyslexia (Galaburda Sherman, Rosen, Aboitiz, & Geschwind, 1985). Findings such as these have begun to reveal a potential mechanistic link between gene and behavior. For example, one proposal, put forth by Giraud and Ramus (2013), posited that abnormal neuronal migration patterns in auditory cortex may alter oscillatory activity in the delta, theta, and low gamma ranges, which correspond to the time scales associated with processing of syllabic stress and may thus play an important role in phonological segmentation, manipulation, and awareness. Two ERP studies of speech processing provide neurogenetic evidence for impaired phonetic processing. Czamara and colleagues (2011) found that one SNP on region on *DCDC2* and two SNPs in regions between *DCDC2* and *KIAA0319* were associated with MMN amplitude (effect size) in a population of German children with dyslexia (Czamara et al., 2011). Further, another SNP in *SLC2A3* (the predominant facilitative glucose transporter not previously associated with dyslexia) was also found to be associated with MMN amplitude in children with dyslexia (Roeske et al., 2011).

A few examples of gene-brain-behavior approaches come from studies of so called generalist genes (i.e., genes proposed to impact a multitude of cognitive systems) (Haworth & Plomin, 2010) in our lab. The first example focused on a well-studied SNP on the *COMT* gene, the Val^{158}Met polymorphism at rs4680, which has been associated with multiple aspects of cognitive function, including auditory function, memory, and attention (e.g., Chen et al., 2004; Egan et al., 2001; Lebedeva et al., 2009). Our studies, which included measuring fMRI activation during reading, and multiple assessments of reading and language skills, found a direct relationship between the *COMT* genotype at this locus, patterns of activity in the brain during reading, and PA skill. Specifically, children with at least one Met allele (Met carriers) outperformed homozygous Val allele carriers on assessments of PA and showed patterns of activation in brain that have previously been associated with better readers (Landi et al., 2013). Follow-up haplotype analyses further confirmed the relationship between *COMT* and PA by identifying haplotypes across two and three SNP combinations of SNPs near rs4680 within the same gene, which were associated with additional reductions in PA, beyond those observed for Val carriers at rs4680 alone (Landi, 2015).

We have also examined the *BDNF* gene, which has an established role in brain maturation and plasticity, specifically, the Val^{66}Met polymorphism in the *BDNF* gene, which affects neural events related to brain plasticity (Cotman & Berchtold, 2002), particularly long-term potentiation (LTP) in the hippocampus. Moreover, *BDNF* gene 13q21 susceptibility alleles have been associated with language impairment (Simmons et al., 2010). We compared reading behavior and functional neural activation in children who were either homozygous carriers of the Val allele (Val/Val; higher levels of BDNF protein) or carriers of the Met allele (Val/Met or Met/Mat; lower levels of BDNF protein). Children who were Met carriers showed poorer behavioral performance on measures of phonological memory and reading comprehension. Further, these children showed increased memory-associated processing (in the hippocampus and parahippocampal cortex) during reading, suggesting greater effort in retrieval of grapheme phoneme correspondences (Jasińska et al., 2016). Taken together, these two studies of so-called generalist genes provide additional evidence for considering a multiple deficit approach that considers the contribution of many neurobiological systems to dyslexia.

Advances in whole exome and whole genome sequencing, in combination with increasing use of network-based approaches to study gene-gene and gene-environment interactions as well as gene-brain–behavior relations are expected to dramatically improve our understanding of causal mechanisms that link genes to brain and behavior across development of this complex disorder. Additionally, whole-systems approaches that include measurement of neurometabolites, in conjunction with traditional imaging approaches and behavioral phenotyping, may help bridge the gap between the levels of gene-brain and behavior. For example, a recent paper from our group reported elevated levels of glutamate and choline, measured with magnetic resonance spectroscopy (MRS) in children with dyslexia (Pugh et al., 2014), providing a potential biomarker for the observed variability and hyperexcitability observed in dyslexic systems. This type of finding can generate new hypotheses for exploring previously unexplored candidate genes and gene-brain-behavior relations.

CONCLUSIONS

The current chapter presents an increasingly accepted view of dyslexia as a heritable, neurobiologically based deficit that is heterogeneous and thus unlikely to be easily reduced to one causal mechanism at the level of gene, brain, or behavior. The majority of individuals with dyslexia have deficits in skills that rely on phonological processing, though the underlying basis of those deficits remains debated. Indeed, some studies have identified deficits at the level of representation (e.g., abnormal categorical perception; Godfrey et al., 1981), and others have found only higher-level deficits (phonological awareness, memory: Ramus & Szenkovits, 2008). Further, some studies have suggested representation-level deficits in processing of amplitude rise times that may manifest as auditory temporal-processing deficits, and give rise to impaired syllable-level processing (Goswami, 2015). Still other lines of research have identified deficits in visual processing or visual attention (Facoetti et al., 2010; Stein & Walsh, 1997), though existing evidence suggests that these deficits are most likely due to reading experience. Moreover, children with multiple deficits (e.g., deficits in both phonological awareness and rapid naming/processing speed), appear to be more severely impaired, and recent neuroimaging work suggests unique neural dysfunction patterns for these two impairments (Norton, Beach, & Gabrieli, 2015).

Neuroimaging studies have identified consistent functional and structural anomaly in left hemisphere brain systems for reading and language in individuals with dyslexia in both the dorsal and ventral language-processing streams (Price & Devlin, 2011; Pugh et al., 2000; Sandak et al., 2004). Further, studies of pre-readers at risk for dyslexia who go on to develop reading problems show similar anomalies in both structure and function (Raschle et al., 2011; Raschle et al., 2012) The most robustly observed neural anomaly at the level of function is hypoactivation in left hemisphere regions, including the fusiform gyrus/occipitotemporal junction, and perisylvian regions during reading (Landi et al., 2010; Pugh et al., 2000). At the level of structure, reduced gray matter volumes in these regions has been routinely observed (Kronbichler et al., 2008). Recent neuroimaging data also strongly implicate abnormal integrity in the arcuate fasciculus in dyslexia (Raschle et al., 2011; Vandermosten et al., 2012), which, combined with intact representation-level phonological processing in left temporal cortex, suggests that the phonological deficits observed in dyslexia may be about access rather than representation (Boets, 2014).

Evidence from behavioral genetic research indicates high levels of heritability for dyslexia, and molecular genetic studies of humans and animals have identified several candidate genes that likely contribute to the biological and behavioral anomalies associated with dyslexia (Grigorenko, 2004). New approaches in molecular genetic analyses are further refining our understanding of the role of particular gene, gene-gene, and gene-environment interactions in dyslexia (Biernacka et al., 2012). And neurogenetic approaches and imaging of neurometabolites have been helpful for identifying how genes may alter neural circuits that result in different dyslexia phenotypes, and in identifying possible new candidate pathways (Landi et al., 2013; Pugh et al., 2014; Roeske et al., 2011).

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CHAPTER 26

SPEECH PERCEPTION

A Perspective from Lateralization, Motorization, and Oscillation

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DEFINITIONAL PRELIMINARIES

Necessary Distinctions

In research on the neurobiological foundations of speech perception, terminology has on occasion been used rather loosely, leading to unnecessary, terminology-induced confusion. Most problematically, the term *speech perception* has regrettably sometimes been used interchangeably with *language comprehension*. We suggest that the expression *language comprehension* ought best be reserved for the sequence of processing sub-routines that occur subsequent to the initial perceptual analyses of some linguistic input. In particular, language comprehension can be subserved by ear, eye, or touch. That is to say, the linguistic system underlying comprehension can be engaged by auditory input (speech), visual input (text or sign), and tactile input (Braille). The processes that form the basis for language comprehension proper therefore build on sensory-input processes that appear to be, at least in part, segregated and independent. The systems and cognitive neuroscience literature contains a number of reports that do not carefully distinguish between these concepts—and therefore conflate the neurocomputational operations responsible for the distinct aspects of perception and comprehension. The focus of the present chapter is, principally, speech perception proper, the perceptual analysis of auditory input. We will provide a brief outline of what we consider a serviceable definition for the cognitive neuroscience of speech perception that links various interrelated questions from acoustics to phonology to lexical access.

Different Experimental Approaches to Speech Perception and Their Consequences

Before turning to a brief definition, and subsequently to the three larger current perspectives on speech perception—the role of hemispheric asymmetry, the role of auditory motor interactions, and the role of neural oscillations—we discuss a few common experimental approaches. We raise these approaches here because several distinctions that become germane in the context of different studies should, in our view, not be overlooked. Broadly speaking, there are at least four experimental approaches that one can group under the rubric *speech perception*. Critically, because the approaches differ substantially with regard to (1) the structure of the input used, (2) the perceptual subroutines under investigation, and (3) the hypothesized end point of the processes, it is important to be sensitive to key differences. First, many experiments use tasks that are executed on individual speech sounds (e.g., single vowels or single syllables); this will be elaborated later. A second type of study exploits lower-level acoustic properties by using non-speech materials that approximate (aspects of) speech, for example, sinewave speech (Remez, Rubin, Pisoni, & Carrell, 1981), noise-vocoded speech (Shannon, Zeng, Kamath, & Ekelid, 1995), frequency-modulated (FM) sweeps (Boemio, Fromm, Braun, & Poeppel, 2005), and other suitable low-level stimuli. Third, speech perception is often investigated in the context of spoken-word recognition using lexical level tasks. This, too, will be expanded later in the chapter. Finally, sentential materials are used to probe speech processing; the view on speech perception from a naturalistic signal perspective has gained popularity in recent years. We will discuss this further, as well.

It should be noted that the experimental approaches and distinctions we point out in the preceding cut across the neural methods that are employed. Whether exploiting the high-spatial resolution of functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume), the high temporal resolution of electroencephalography (EEG; see Leckey & Federmeier, Chapter 3 in this volume), magnetoencephalography (MEG; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume), and electrocorticography (ECoG), the dissociation logic of neuropsychological deficit-lesion studies, or the causal manipulations investigated with transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume), the questions surrounding speech perception have been addressed with each technique and at each level of analysis, from single vowels to single words to connected spoken sentences. The diversity of findings requires that one be especially careful about the decomposition of the tasks and the materials and the putative representations and computations that are in fact implicated in a given study.

A large body of research on speech perception works with specific contrasts across individual speech sounds (i.e. sub-lexical/pre-lexical units of speech). Participants are typically presented with single vowels or single syllables and are asked to execute some particular task (e.g., discrimination or identification). In a typical study design, participants listen to consonant-vowel (CV) syllables drawn from some acoustic continuum—for example, stimuli drawn from the /ra/-/la/ tongue-shape contrast or the /bi/-/pi/ voicing contrast—and are asked upon presentation of a single stimulus to identify the category. These questions focus on sub-lexical properties of speech and examine, for example, questions concerning categorical perception in speech, the phonemic inventory of speakers/listeners of different languages, perceptual magnet effects, the changes associated with first- and second-language learning, phonotactic constraints, the role of distinctive features, and other issues reasonably addressed at the pre-lexical level of analysis.

This avenue of research has been very productive in the behavioral literature and is also prominent in the cognitive neurosciences. Using fMRI, for example, several labs have examined regionally specific hemodynamic effects when participants make judgments on categorically varying stimuli (Blumstein, Myers, & Rissman, 2005; Chang et al., 2010; Liebenthal, Binder, Spitzer, Possing, & Medler, 2005; Raizada & Poldrack, 2007;). These studies show that there are cortical regions responding differentially to signals that belong to different categories, or that are speech versus non-speech. It is noteworthy that no simple answer has resulted from a group of rather similar studies (at least at the surface). Temporal, parietal, and frontal brain areas have all been implicated. Similarly, electrophysiological techniques (EEG, MEG) have been used to probe the phonemic inventories of speakers of different languages. Näätänen et al. (1997) were able to show subtle neurophysiological distinctions that reflect the vowel inventories of Finnish versus Estonian speakers. Kazanina, Phillips, and Idsardi (2006) used MEG recordings to illustrate how language-specific contrasts (here Russian vs. Korean), including allophonic distinctions, can be measured neurophysiologically.

This research program has had considerable influence, but it also has important limitations. For example, a very large number of experiments test categorical perception—as well as the notion of "rapid temporal processing." These are typically based on plosive contrasts (especially voice-onset time, VOT). While it is true that syllables with plosive onsets are fascinating in their acoustic complexity (and VOT is easily manipulated), a variety of other phenomena at the pre-lexical level have not been explored very well. Also, these types of studies are, in some sense, "maximally ecologically invalid." Experimenters present single, sub-lexical segments of speech in the context of experimental tasks that require attention to some particular feature. The tasks by and large engage no (or only very limited) further linguistic processing. The results from such experiments are in danger of capturing the processes underlying ecologically natural speech perception in a very limited way, at best. Listeners do not (consciously) attend to sub-lexical material; therefore, the interpretation of such results requires a great deal of caution because task effects are known to modulate neural reactivity in very dramatic ways, modulating, for example, response amplitudes and even hemispheric asymmetry (e.g., Poeppel et al., 1996).

Another line of research tests speech perception through the lens of spoken word recognition. There exists a range of lexical access models (e.g., lexical access from spectra, Klatt, 1979, 1989; TRACE, McClelland & Elman, 1986; instantiations of the cohort model, e.g., Gaskell & Marslen-Wilson, 2002; the neighborhood activation model, Luce & Pisoni, 1998; continuous mapping models, Allopenna, Magnuson, & Tanenhaus, 1998, and others). These have provided critical information regarding the structure of the mental/neural representations of, informally speaking, words. The most typical experimental manipulations include lexical decision, naming, gating, and priming. Recognizing single spoken words is more natural than performing atypical task demands on sub-lexical material.

Influential cognitive neuroscience contributions to this area have been made by Blumstein and colleagues, who have examined spoken-word recognition using deficit-lesion approaches and imaging data (e.g., Utman, Blumstein, & Sullivan, 2001; Misiurski, Blumstein, Rissman, & Berman, 2005; Prabhakaran, Blumstein, Myers, Hutchison, & Britton, 2006; see Blumstein, Chapter 1 in this volume). They support a model in which superior temporal cortex areas mediate acoustic-phonetic analyses, temporo-parietal areas perform the "mapping" from acoustics to phonological-lexical representations, and frontal areas (specifically the inferior frontal gyrus) play a role in resolving competition (i.e., deciding between alternatives when listeners are exposed to noisy or underspecified input). In addition, the effect of lexical status on speech-sound categorization has been investigated in the behavioral literature (typically in the context of evaluating top-down effects), and Myers and Blumstein, using voicing continua with word or nonword end points, have extended this work using fMRI (Myers & Blumstein, 2008). They demonstrate fMRI-based dissociations between functionally earlier effects in the temporal lobes (arguably related to perceptual analyses) and later, downstream decision processes implicating frontal lobe structures. One behavioral task that has been used productively in studies of lexical representation is repetition priming. Gagnepain et al. (2008) used word and nonword repetition priming to elucidate which cortical structures are specifically sensitive to the activation of lexical entries (for an MEG implementation of this design, see Almeida & Poeppel, 2013). Bilateral superior temporal sulcus (STS) and superior temporal gyrus (STG) were particularly prominent, suggesting that the mapping to lexical information occurs in cortical regions slightly more ventral than perceptual computations (cf. Hickok & Poeppel, 2000, 2004, 2007).

A third way in which speech perception is increasingly examined is to use natural spoken sentences, sometimes explicitly to assess their intelligibility if a task is desired, and sometimes under conditions of passive listening (the most naturalistic condition). In such experiments, participants are presented with sentences (sometimes having undergone acoustic manipulations) and are asked to provide some estimate of intelligibility (e.g., by reporting keywords). Understanding spoken sentences is an important goal because it is the perceptual situation we most want to explain. However, there is a big price to pay for using ecologically natural materials: it becomes quite difficult to isolate input-related perceptual processes per se, because the presentation of sentences necessarily entails lexical access processes, syntactic processes, both lexical semantic and compositional semantic processes, and so on. Numerous "top-down" factors—that play a critical role in the overall analysis of spoken input—are all concurrently engaged.

Virtually all cognitive neuroscience recording techniques have been used to test intelligibility at the sentence level (see Bornkessel-Schlesewsky & Schlesewsky, Chapter 27 in this volume). Based on a series of positron emission tomography (PET) and fMRI studies, Scott and colleagues show that anterior temporal lobe structures, especially anterior STS, play a privileged role in mediating intelligibility (e.g., Scott Blank, Rosen, & Wise, 2000). Electrophysiological techniques have also been used to study sentence-level intelligibility. Luo and Poeppel (2007), for example, argue that phase information in the cortical signal of a particular frequency, the theta band, is closely related to and modulated by the acoustics of sentences (this is discussed in more detail later in the chapter). A nice link between spoken-sentence processing and low-level speech analysis was recently demonstrated by the electrophysiological experiment of Mesgarani, Cheung, Johnson, and Chang (2014). Pre-surgical epilepsy patients with implanted grids listened to spoken sentences. The electrocorticographic data were analyzed, with special attention to the local speech segments (i.e., the phonemic level). By way of innovative analysis approaches, the authors found support for the relevance of low-level features: the data from STG were consistent with the view that neural activation patterns reflect an encoding of distinctive features as the building blocks of phonemic processing.

In summary, the expression *speech perception* is used in at least three ways. Important aspects of the neurocognitive system underlying speech and language have been discovered using all three approaches. This brief perspective serves to remind the reader that it is challenging to isolate the relevant perceptual computations. Clearly, we need to turn to all forms of experimental approaches to obtain a comprehensive characterization. For example, to understand the nature of distinctive features for perception and representation, experimentation at the level of sub-phonemic, phonemic, or syllabic levels is critical; to elucidate how words are represented and accessed, research on spoken-word recognition is required; and it goes without saying that we cannot do so without investigating the comprehension of spoken sentences.

Attempt at a Definition of Speech Perception Linking across Levels

The perspective summarized in brief here has been developed more fully elsewhere (Poeppel & Hackl, 2008; Poeppel, Idsardi, & van Wass, 2008; Poeppel & Monahan, 2008). Figure 26.1, adapted from Poeppel et al. (2008), summarizes what we take to be the perceptual challenge. We take speech perception to refer to a specific set of computational sub-routines: speech perception comprises the set of operations that take as input continuously varying acoustic waveforms made available at the auditory periphery and that generate as output those representations (morphemic, lexical) that constitute the data structures for subsequent operations mediating language comprehension. More colloquially speaking, this view can be caricatured as “the collection of operations that lead from vibrations in the ear to abstractions in head” (or from “Sounds in the Cochlea to Morphemes in Cortex”—SoCoMoCo).

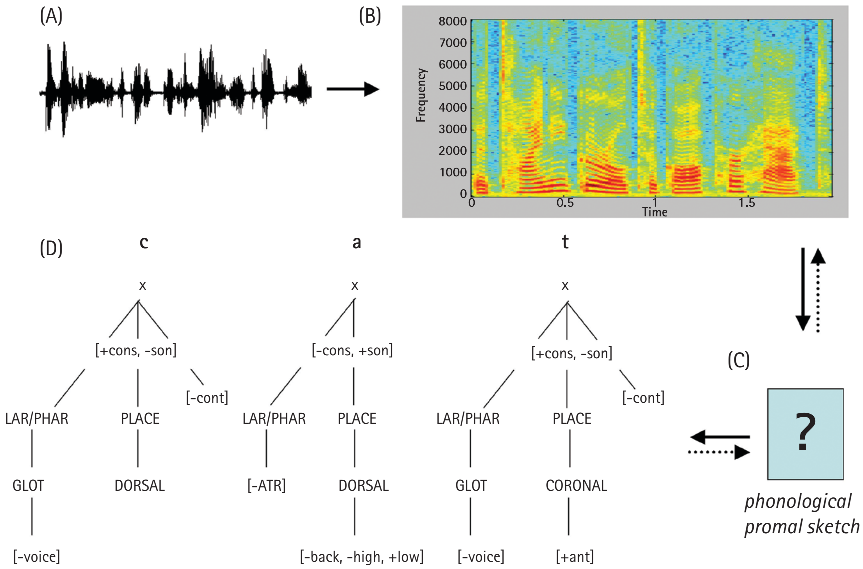

FIGURE 26.1. From waveforms to words. Continuously varying acoustic signals (A) are analyzed in the afferent auditory system. The analysis streams yield "neural versions" of spectrograms (spectrotemporally specified representations) in bilateral auditory cortex (B) Based on this high-resolution cochleogram representation, we hypothesize that a "primal sketch"—based on multi-time resolution analysis of the information contained in (B)—is constructed (C). The perceptual goal or end game is the identification of words, which we take to be represented in memory as sequences of segments that themselves are composed of bundles of distinctive features, here exemplified as the word [cat] (D).

Source: From Poeppel, Idsardi, and van Wassenhove (2008).

The starting point, the acoustic signal, is a continuously varying waveform that encodes information on different timescales (Figure 26.1 A). For example, the amplitude envelope of a signal (which can be investigated as a broadband signal or by cochlear channels or critical bands) correlates well with properties of the syllabic sequence of an utterance. The fine structure of a signal, in contrast, carries information over shorter time scales (including features and segments). This input data stream must, in the end, be transformed into a sequence of discrete segments that constitute a stored morpheme (or informally, a word). Because we believe the central goal to be the identification of spoken words, specifying the format of the stored lexical representation becomes necessary. In particular, the morphemes/words must be stored in a format that permits them to enter into linguistic computation (including, most critically, the combinatoric operations that underlie language comprehension). Identifying a word is obviously not enough—the listener must (be able to) connect it formally (in terms of representational specifications, i.e., noun, determiner, etc., in whatever neural code that is specified in) to its neighboring environment. This is required to perform the phonological, morphological, syntactic, or semantic operations the situation demands—and which we know take place. We adopt the view here, developed in linguistic research over the last decades—and implicit since the Phoenicians invented an alphabet—that lexical representations are represented as a series of segments; segments themselves are made up of bundles of features (Figure 26.1 D). We explicitly will also allow other, parallel representations (e.g., the notion of a syllable).

The initial input waveform is analyzed by the auditory periphery and presumably represented in auditory cortex by neurons with spectrotemporal receptive field properties (STRFs) covering a range of relevant sound modulations. This can be thought of as a neural version of a spectrogram, although a version composed of numerous mini-spectrograms, encompassing specializations for certain spectrotemporal patterns (Figure 26.1 B). (Given the highly conserved nature of mammalian auditory cortex, these representations are likely shared with other species, and consequently can be investigated fruitfully using animal models.) Based on such initial (rather high spectrotemporal resolution) auditory cortical patterns, multiple representations on different time and frequency scales are constructed, in parallel. In such a next step, "auditory primitives" are built out of early auditory cortical elements, with a key feature being the time scale of the new representations. This third type of representation must be of a granularity that permits mappings (linking procedures) from simple acoustic properties in early auditory cortical areas to speech primitives in more downstream areas (arguably STG and STS). We hypothesize that these intermediate representations encompass at least two subtypes, commensurate with syllabic and segmental durations, respectively (Boemio et al., 2005; Giraud et al., 2007; Poeppel, 2001, 2003; Poeppel et al., 2008). The initial cortical representation is segregated into (at least) two parallel processing streams, and concurrent multi-time resolution analysis then lies at the basis of subsequent steps. The specific nature of this intermediate representation is a critical research question; one might characterize the question as arriving at a "primal sketch" for speech perception (Figure 26.1 C), related to David Marr's famous hypothesis about intermediate representations for visual object recognition.

One specific possibility for a primal sketch is a PFNA (plosive-fricative-nasal-approximant) coarse coding. Let us hypothesize that this code is just the speech stream roughly encoded into the four categories of PFNA. Preliminary modeling of English-like lexica shows that this coarse coding yields pools of words of approximately the same size as the typical lexical neighborhoods, with a fair degree of overlap between neighborhoods. We now stipulate a directed left-to-right search, using contextually defined featural definitions. Importantly, this search—after having found broad landmarks—can be guided by the differences among the words in the active neighborhood by using analysis-by-synthesis and/or Bayesian inference. Finally, once the best-available target has been selected, the content of that lexical item is examined, compared to the trace of the incoming signal, and verified to be the word being sought.

The final, featurally specified representation is by hypothesis the format that is both the end point of speech perception, which is also the set of instructions for possible articulation. The loop between perception, memory, and action is enabled in such a scheme because the representational format used for words in memory, distinctive features, allows the mapping both from the input waveform to words and from words to motoric action (features are in motor coordinates). In conclusion, we envision a three-step process that offers a computational locus for the kinds of findings typical of speech perception research: from early encoding and sensitivity to acoustics, to various lexical effects, to links to the motor system. We now turn to broader issues that have received a great deal of attention in the cognitive neuroscience literature.

HEMISPHERIC ASYMMETRIES

One of the most striking examples of functional lateralization in cortex is that damage to the left hemisphere quite often produces a severe impairment to language processing, while damage to the right hemisphere does not. The lateralization of language to the left hemisphere has been consistently reported ever since the pioneering work of Paul Broca and Carl Wernicke in the nineteenth century (Broca, 1861; Wernicke, 1874; see Van der Haegen & Cai, Chapter 34 in this volume). Despite 150 years of research, elucidating hemispheric dominance in healthy participants is surprisingly difficult and, in clinical contexts, still requires an intra-carotid injection of sodium amytal to each hemisphere separately (Wada, 1949). Laterality of function has been extensively demonstrated using psychophysical measures, electrophysiology, and neuroimaging—but the exact underpinnings of the cortical architecture and its asymmetric nature remain elusive. Behaviorally, participants are more accurate in reporting stimuli presented to the right ear compared with the left ear in a dichotic listening paradigm (Kimura, 1967). This right ear advantage (REA) is highly modulated by attention and is only partially concordant with Wada-test results (Hugdahl, 2011). There is an ongoing effort to introduce neuroimaging as part of preoperative language mapping; nevertheless, studies report that 15%–20% of patients show discordant results with the Wada test (Bauer, Reitsma, Houweling, Ferrier, & Ramsey, 2014; Janecek et al., 2013), and it remains controversial whether noninvasive measures are sufficient for mapping language dominance (McDonald, Kean, & Saykin, 2011; Papanicolaou et al., 2014).

Evidence for hemispheric specialization exists early in development. Near-infrared spectroscopy in *neonates* demonstrates an asymmetric hemodynamic response profile to repetition-based structures in syllable sequences (Gervain, Macagno, Cogoi, Peña, & Mehler, 2008), to phonemic and prosodic cues in word stimuli (Arimitsu et al., 2011), as well as to temporal modulations in speech-inspired non-speech stimuli (Telkemeyer et al., 2009). It is debated to what degree these putative specializations change across development. For example, Telkemeyer et al. (2011) argue that left and right temporal cortex sensitivity to acoustic temporal modulations remains stable as infants mature from neonates (Telkemeyer et al., 2009) to infants (Telkemeyer et al., 2011), while data from Arimitsu et al. provide evidence that temporal cortex sensitivity to phonemic cues is symmetrically bilateral and an asymmetric shift toward increased left sensitivity occurs at age 11–12 months (Arimitsu et al., 2011).

Since the seminal findings of Carl Wernicke, localizing language comprehension deficits to the left posterior temporal cortex, the perceptual analysis of language has been mostly considered a left hemisphere capacity (Geschwind, 1970; Wernicke, 1874). Observations starting in the second half of the twentieth century have shed light on the contributions of different features, painting a more complicated picture of the underlying cortical structures involved in processing speech. Studies in aphasic patients implicated the left temporal lobe in processing temporal order (Efron, 1963) as well as specific temporal cues (Carpenter & Rutherford, 1973; Schwartz & Tallal, 1980), formant transitions (Tallal & Piercy, 1975), and voice onset time (Blumstein, Cooper, Zurif, & Caramazza, 1977). These deficits in temporal processing were often contrasted with the spared ability to discriminate spectral cues (Carpenter & Rutherford, 1973). Around the same time, evidence emerged that focal damage to the right hemisphere produced impairments in processing prosodic aspects of speech (Ross & Mesulam, 1979; Tucker, Watson, Heilman, 1977), and later studies also implicated the right hemisphere in processing spectral cues (Robin, Tranel, & Damasio, 1990; Zatorre, 1988).

Based on these findings, as well as early neuroimaging studies (Belin et al., 1998; Zatorre, Evans, Meyer, & Gjedde, 1992), an influential framework emerged whereby the left hemisphere is more sensitive to temporal cues, whereas the right hemisphere is more sensitive to spectral cues (Zatorre, Belin, & Penhune, 2002). A complementary framework explains the differences in auditory sensitivity as a function of temporal integration windows, whereby the left hemisphere preferentially integrates over shorter timescales (20–80 ms) and the right hemisphere preferentially integrates longer timescales (150–300 ms) (Poeppel, 2003). Both the Zatorre and Poeppel views, which are very similar, have been debated and contested; for example, Scott et al. argue that while the right temporal cortex is highly selective to acoustic features and is domain general, the acoustic selectivity of the left hemisphere is weak at best and is rather driven by speech sounds, which are domain-specific and have a more complex acoustic characterization (McGettigan & Scott, 2012; Scott & McGettigan, 2013).

The advent of neuroimaging techniques gave rise to numerous studies trying to elucidate the functional anatomy of auditory, speech, and language processing. A recurring finding has been the bilateral involvement of the STG in processing speech sounds (Binder et al., 1997; Hirano et al., 1997; Mazoyer et al., 1993; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Wise et al., 1991), with preferential recruitment of left hemisphere structures depending on how stimuli were controlled and contrasted, and the demands of the tasks employed (Binder et al., 2000; Hickok & Poeppel, 2007; Price, 2012; Scott, Blank, Rosen, & Wise, 2000). Listening to non-speech stimuli has consistently shown bilateral responses characterized by an asymmetry in response to stimuli, varying along spectral and temporal dimensions. Neuroimaging studies have reported a greater sensitivity in the left hemisphere to a temporal gradient (the rate of alternating two pure tones), in contrast to a greater sensitivity in the right hemisphere to a spectral gradient (the number of alternating pure tones varying in frequency) (Jamison, Watkins, Bishop, & Matthews, 2006; Zatorre & Belin, 2001). Similar lateralized responses have been observed in neurophysiological data in response to spectral change (stimulus changes in frequency) or temporal change (stimulus changes in amplitude modulation) (Okamoto & Kakigi, 2013; Okamoto, Stracke, Draganova, & Pantev, 2009).

Evidence from passive listening paradigms using both neuroimaging (Boemio et al., 2005; Telkemeyer et al., 2009) and neurophysiology (Luo & Poeppel, 2012) shows asymmetric responses as a function of a temporal axis. Both left and right temporal cortices responded similarly to stimuli consisting of concatenated short segments (~25–50 ms), while a preferential response in right temporal cortex was reported for stimuli consisting of long segments (~150–300 ms). Similarly, studies have shown enhanced right hemisphere sensitivity to features such as spectral correlation (Overath, Kumar, Kriegstein von, & Griffiths, 2008), where increased correlations across frequency components are equivalent to longer temporal windows, as well as pitch discrimination (Hyde, Peretz, & Zatorre, 2008). Systematically varying the temporal modulations of acoustic stimuli has shown a low-pass characteristic bilaterally (Liégeois-Chauvel, Lorenzi, Trébuchon, Régis, & Chauvel, 2004; Overath, Zhang, Sanes, & Poeppel, 2012; Wang et al., 2012), with reports of the left hemisphere covarying with temporal modulations (Schönwiesner, Rübsamen, & Cramon Von, 2005), as well as left hemisphere increased sensitivity to slower temporal modulations (Liégeois-Chauvel et al., 2004; Wang et al., 2012). Recently, studies have reported a spatial topography of auditory cortex sensitivity to temporal and spectral modulations (Barton, Venezia, Saberi, Hickok, & Brewer, 2012; Herdener et al., 2013; Joanisse & DeSouza, 2014; Santoro et al., 2014; Schönwiesner & Zatorre, 2009). While these studies have reported mostly bilateral symmetries, modulation topographies show conflicting results (Herdener et al., 2013; Santoro et al., 2014; Schönwiesner & Zatorre, 2009), as well as conflicting reports of frequency modulation encoding, which in some cases was only revealed using multi-voxel pattern analysis (Hsieh, Fillmore, Rong, Hickok, & Saberi, 2012; Joanisse & DeSouza, 2014). The exact spatial topographic distribution of combined spectral-temporal modulations remains to be clarified—as well as how these maps relate to functional hemispheric asymmetries.

The acoustic spectrotemporal features that drive hemispheric responses are closely related to speech-specific features that have been reported in the left hemisphere, such as voicing (Liégeois-Chauvel, de Graaf, Laguitton, & Chauvel, 1999; Steinschneider et al., 2005; Trébuchon-Da Fonseca, Giraud, Badier, Chauvel, & Liégeois-Chauvel, 2005) and place of articulation (Arsenault & Buchsbaum, 2015; Chang et al., 2010; Kilian-Hütten, Valente, Vroomen, & Formisano, 2011). In the case of speech, these acoustic and phonetic features do not exist in a vacuum, but are rather an integral part of connected speech and the basis for engaging semantic and syntactic systems. In that context, Obleser et al. report that degrading speech intelligibility along temporal (reducing temporal modulations) and spectral (reducing the number of spectral bands) axes drives the left and right superior temporal sulcus, respectively, but the left hemisphere was equally affected by the temporal and spectral manipulations (Obleser, Eisner, & Kotz, 2008). Similarly, neuroimaging studies have consistently reported that degrading the intelligibility of speech stimuli shows a strong left hemisphere bias (Obleser, Meyer, & Friederici, 2011; Obleser, Wise, Dresner, & Scott, 2007; Rosen, Wise, Chadha, Conway, & Scott, 2011; Scott et al., 2000), although the right hemisphere sensitivity to spectral features is debated (McGettigan & Scott, 2012; Zatorre & Gandour, 2008). Electrophysiological findings have shown that the phase of cortical theta oscillations (~4–8 Hz) reliably tracks and discriminates sentences (Luo & Poeppel, 2007), is modulated by attention (Kerlin, Shahin, & Miller, 2010), and shows enhanced phase-locking to the envelope (modulation of signal energy over time) of intelligible sentences (Peelle, Gross, & Davis, 2013). Phase-locking occurs bilaterally, and while intelligible sentences showed left hemisphere enhanced locking (Peelle et al., 2013), sentence-discrimination effects were driven by the right hemisphere (Kerlin et al., 2010; Luo & Poeppel, 2007). This right hemisphere theta effect is consistent with a literature supporting its role in segmenting the speech signal with a window of ~200 ms, while the increased effect of intelligibility provides evidence for interaction with other linguistic systems in the left hemisphere (Giraud & Poeppel, 2012; Millman, Woods, & Quinlan, 2011; Morillon et al., 2010).

It is now well established that speech is processed bilaterally but becomes increasingly lateralized to the left with higher-order linguistic input (Binder et al., 2000; Friederici, 2011; Giraud & Poeppel, 2012; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). Nevertheless, whether or not this asymmetry is driven by acoustic features in addition to linguistic factors—as well as the exact computational framework—remains vigorously debated (Giraud & Poeppel, 2012; Obleser, Herrmann, & Henry, 2012; Peelle, 2012; Scott & McGettigan, 2013; Zatorre & Gandour, 2008).

THE ROLE OF THE MOTOR SYSTEM

The two primary modalities for speech are auditory input for perception (listening) and motor output for production (speaking). Early work by neurologists in the nineteenth century proposed that these two processes were also separate neuroanatomically (Broca, 1861; Lichtheim, 1885; Wernicke, 1874). The neural substrate for production was proposed to be in the inferior frontal cortex, whereas perception was localized to the posterior STG and STS. The major assumptions were therefore twofold: first, that there were clearly definable and separate areas for production and perception; and second, that the representations underlying these processes were also separable.

This latter proposed segregation of function was challenged by proposals for a strong role for production-related processes during speech perception. This was the position put forth by Liberman and colleagues with the motor theory of speech perception (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967; Liberman, Cooper, Studdert-Kennedy, Harris, & Shankweiler, 1968; Liberman & Mattingly, 1985). They argued that the underlying perceptual speech representations were in fact "intended articulatory gestures" for speaking. Liberman and colleagues found that when presenting a noise burst at a particular frequency, it was perceived as either a /k/ or a /p/ depending on the subsequent vowel (Cooper, Delattre, Liberman, Borst, & Gerstman, 1952; Liberman, Delattre, & Cooper, 1952). They argued that this constituted evidence against a purely acoustic theory of perception, and supported a model that involved reconstructing the intended outgoing motoric gesture (Liberman & Mattingly, 1985; Liberman et al., 1968). These gestures were proposed to be the elementary units of speech, and consequently, defining their feature space was seen as a central goal of studying the neural representation of speech.

The focus of the motor theory shifted from a purely motor involvement in perception to a unified "phonetic" module for speech, in line with proposals for the modularity of mind (Fodor, 1983). The "phonetic" module was argued to be responsible for processing speech-specific information, which differed from purely acoustic information (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967). Through this proposal, representational processes that underlie both perception and production were united. This contrasted with theories based on earlier lesion work by the nineteenth-century neuroanatomists that argued for a stricter separation.

Initial evidence for this lack of perception/production separation comes from the work of Sheila Blumstein and colleagues starting in the 1970s. Contrary to what a strong anterior/posterior production/perception split would predict, both Broca's and Wernicke's aphasics display production errors (Blumstein, 1994). Both classes of aphasics also demonstrate perceptual deficits, specifically on discriminating phonological contrasts (Blumstein, Cooper, Zurif, & Caramazza, 1977). Furthermore, both classes of aphasics make articulatory errors (Blumstein, 1994).

Further evidence for this unified theory has since been added from two other sources. The first comes from perceptual difficulties in instances where the articulatory system is compromised. The second is neuroimaging evidence that seeks to relate the anatomy associated with production during perceptual processing. With respect to the first source of evidence, there have been several reports that perceptual deficits follow articulatory ones. Bridgeman and Snowling (1988) found that when comparing children with dyspraxia and their age- and reading-ability-matched controls, the dyspraxic group was worse at discriminating nonwords in a same/different task, while no such difference was found for real words. The authors argue that this is evidence for a dual route of processing in which a lexical route (intact in both groups) processes lexical input, and a non-lexical phonetic stream (deficient in the dyspraxic children) processes novel/nonword input. Using a series of rhyme-based tasks, Marion Sussman, and Marquardt (1993) found that dyspraxic children had difficulty producing and perceiving rhymes compared to controls. Specifically, they produced far fewer rhyming words when prompted with a token, were less able to recognize rhyme pairs, and were also worse at judging vowel similarity (a result that was also echoed by Maassen Groenen, & Crul, 2003). The authors conclude that this is evidence for a deficit in a higher-order phonemic mechanism that is shared between perception and production. Nijland (2009) found that, like the previously mentioned studies, children with apraxia were worse at nonword discrimination and rhyming judgments. She also found that these tasks demonstrated a significant link to production via a positive correlation with nonword repetition. In sum, behavioral perceptual deficits associated with clinical articulatory deficits demonstrate that there is a tight link between processes that underlie perception and production. The locus of these behavioral deficits seems to be focused on the role of (faulty) articulation and its role in the development of phonetic/phonemic (sub-lexical) processing.

From a neurophysiological standpoint, there have been several demonstrations of activation of the premotor/motor cortex during passive listening to speech using both ECoG and fMRI (Cogan et al., 2014; Pulvermüller et al., 2006; Wilson, Saygin, Sereno, & Iacoboni, 2004). Du et al. (Du, Buchsbaum, Grady, & Alain, 2014) used fMRI to test the activation of motor areas during speech perception. Specifically, they found that the BOLD response in the premotor cortex exhibited a negative correlation with behavioral accuracy of a phoneme identification task in increasing amounts of background noise, demonstrating greater premotor cortex activation in noisier conditions. Furthermore, using multivoxel pattern analysis (MVPA), they found that the identity of the phoneme could be determined in lower signal-to-noise ratios (SNR) in the premotor cortex compared to a speech-sensitive auditory area (STS).

There have also been TMS studies that argue for a causal role of motor areas during perception. Meister, Wilson, Deblieck, Wu, and Iacoboni (2007) used TMS over the left premotor cortex to demonstrate that stimulation resulted in poorer phoneme discrimination in noise. A widely cited example of linkage between neural motor processes and perception is from a study by D'Ausilio et al. (2009) in which TMS was applied to both the lip and tongue areas of the primary motor cortex (M1). Their results suggested a double disassociation during identification of syllables starting with one of four plosives (/b/, /p/, /d/, /t/) in which stimulation to the tongue area of M1 disrupted /d/ and /t/ identifications, and stimulation to the lip region disrupted identification of /b/ and /p/ , suggesting a link between the perception of phonemes and the articulatory apparatus that specifically produces them. It is worth noting that the stimuli in this study were also presented in noise. This result was supported in a TMS study by Fadiga et al. (Fadiga, Craighero, Buccino, & Rizzolatti, 2002) in which motor-evoked potentials (MEP) were measured in the tongue during speech perception. Results implied an increase in amplitude of the tongue MEPs during the passive listening of disyllabic words and pseudowords containing either /f.f/ (labiodental fricative—slight tongue tip movement) or /r.r/ (trill—more tongue tip movement). There were higher amplitude MEPs on the tongue during TMS stimulation for words and pseudowords containing /r.r/ compared to /f.f/. This further suggests a link between the perception of phonemes and activation of the corresponding articulatory mechanisms that produce them.

Cumulatively, these results argue for a *potential* role for the motor system during speech-perception tasks, in particular focused on sub-lexical phonetic processing. Phonetic task differences in children with dyspraxia provide behavioral evidence for a motor involvement in speech perception, and various imaging (fMRI, ECoG) and stimulation (TMS) results demonstrate that the motor system affects perceptual abilities. The most likely candidate for the locus of this linkage is sub-lexical. This would provide a plausible basis for linking motor gestures with perception (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967). What remains unclear is the *necessity* of the motor system in perception. Given that the majority of neuroimaging and stimulation results were presented in noise, it could be that the motor system is recruited specifically in instances in which some form of supplementary processing is required. The role of the motor system could therefore be *more modulatory rather than causal* (Hickok, 2009). The motor system could, for example, be recruited via a non-lexical route to aid perception during noisy or ambiguous situations.

A different class of proposals argues against the sub-lexical perception/production link and instead posits that the role of the motor system in speech perception relates to the meaning of words. Specifically, it is argued that the motor system represents words that are semantically congruent with the actions performed by the particular effectors controlled by the motor system (e.g., *lick*: tongue; *kick*: leg). This approach is based heavily in the broader theory of embodied cognition (Rosch, Thompson, & Valera, 1992) where complex cognition is carried out through the same processes that underlie action. Through this approach, action and perception are linked not at the implementational level (i.e., through a link with the articulatory system), but rather at the abstract level. The motor system's role in speech, therefore, would be to provide a causal instantiation of the semantic space of words. In other words, conceptual knowledge about actions shares the same circuits as the motor programs for these actions.

Linkage at this level was suggested by Hauk, Johnsrude, and Pulvermüller(2004), who found that when subjects were visually presented with action words that were related to movements associated with specific effectors (e.g., *leg, arm*), they demonstrated higher BOLD activation in their correspondent motor region in the motor cortex and prefrontal cortex. This basic finding has also been explored using EEG (Shtyrov, Hauk, & Pulvermüller, 2004) and MEG (Pulvermüller, Shtyrov, & Ilmoniemi, 2005). A more recent study, however, using ECoG did not replicate this effect (Canolty et al., 2007). The main drawback of such theories is that they fail to account for all but a very restricted class of linguistic materials. Concepts that are not directly related to human action (or their figurative counterparts (Fernandino et al., 2013) are not easily accounted for using this model.

Neurophysiological arguments for a motor-centric view comes from the more recent mirror neuron findings in humans. Mirror neurons fire both when an action is perceived and when an action is being executed. They were first demonstrated in the macaque area F5 (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). Similar response profiles have since been identified in humans in the inferior frontal gyrus (Kilner, Neal, Weiskopf, Friston, & Frith, 2009) using fMRI and in the supplementary motor area (SMA) using single-unit recordings (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). These mirror neurons also respond to the sound of actions as well as their sight (Kohler et al., 2002), suggesting a higher-order level of abstraction. It is worth noting that these neurons respond also when a goal-directed action is taking place and is not visually present, suggesting that the representation is not purely due to the external stimulus (Umiltà et al., 2001). Furthermore, different populations of mirror neurons in the inferior parietal lobule (IPL) respond differently to the same movement depending on the context of the action, suggesting that this system could be used to differentiate between higher-order actions (Fogassi et al., 2005).

On the face of it, the mirror neuron system seems to be a plausible substrate for higher-order semantic-based representations in the motor system. The higher-order representational properties of such cells could support a system that operates at the level of conceptual (or, in humans, even lexical) semantics. However, the locus of representation could in theory be any complex directed representation. This is especially important given that the initial proposed representation of the motor theory of speech was claimed to be the intended motor gesture (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967; Liberman & Mattingly, 1985). It could therefore be—assuming there is a relationship between the mirror system and speech—that the representational substrate that it operates on is at the level of phonetics rather than semantics. The mirror system therefore, provides at best an ambiguous neural substrate for a semantic role for the motor system in speech perception.

There does exist convincing evidence for a linkage between motor output and sensory input systems for speech, certainly under particular processing circumstances. Mapping between the sensory system and the motor system could operate to form a unified sublexical representation for the speech system (Cogan et al., 2014). The engagement of the motor system would therefore reflect part of a unified phonetic system (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967; Liberman & Mattingly, 1985). In sum, there is evidence that the motor system is active during speech perception. While there is some evidence that the role of the motor system in speech perception is to represent, in semantic terms, action words (Pulvermüller, 2005), there is stronger evidence that the locus is the phonetic level. Cumulatively, the behavioral, lesion, and neurophysiological evidence suggests that at the phonetic level, the original strong segregation of function between production and perception in speech processing is no longer tenable. That being said, a comprehensive, theoretically persuasive, and mechanistic model does not yet exist.

Cortical Oscillations in Speech Perception

There has been a substantial interest in the phenomenon of neural oscillations and their potential role in attention (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008), memory (Gruber, Tsivilis, Giabbiconi, & Muller, 2008; Palva, Palva, & Kaila, 2005), decision-making (Guggisberg, Dalal, Findlay, & Nagarajan, 2007), and speech perception (Ahissar et al., 2001; Lalor & Foxe, 2010; Luo & Poeppel, 2007; Peelle, Gross, & Davis, 2013). Neural oscillations reflect physiological excitability cycles and occur in multiple time scales that emerge from the biophysical properties of neural ensembles. These time scales extend over a wide range, from very slow fluctuations (<1 Hz) to very fast ones (>100 Hz) (Buzsáki & Draguhn, 2004; Fries, 2005). One hypothesis is that these time scales relate to exogenous phenomena that occur at corresponding time frames

(Giraud & Poeppel, 2012; Poeppel, 2003). In the case of speech, there is a striking correspondence between the time scales of phonemic, syllabic, and phrasal processing, on the one hand, and low gamma (30–50 Hz), theta (4–8 Hz), and delta (<3 Hz) oscillations in auditory cortex, on the other. This correspondence has led to the hypothesis that cortical oscillations play an active role in "sampling" (or "parsing" or "segmenting" or "chunking") the continuous speech signal into meaningful linguistic units (Ghitza, 2011; Ghitza, Giraud, & Poeppel, 2012; Giraud & Poeppel, 2012).

Giraud and Poeppel (2012) have suggested an oscillation-based processing model that hypothesizes a cascade of processes leading from connected speech to a discrete code (Figure 26.2). In this model, intrinsic slow (<10 Hz) oscillations in auditory cortex phase-lock to incoming speech such that the activity in the theta band, in particular, tracks the envelope (energy fluctuations over time) of speech. Next, through a mechanism of cross-frequency coupling, the phase of theta oscillations determines the amplitude of gamma oscillations. Finally, gamma oscillations regulate spiking activity such that neural excitability is aligned with speech modulations (see Figure 26.2).

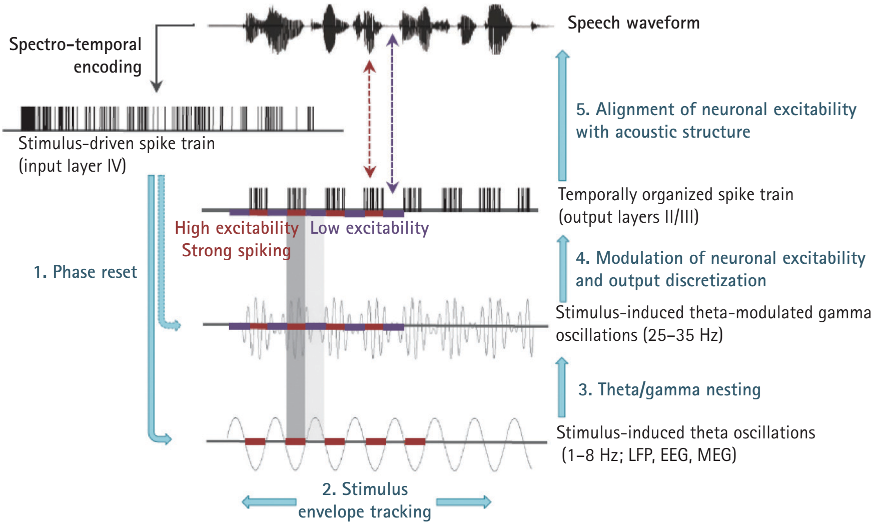
Speech waveform
Spectro-temporal encoding
Stimulus-driven spike train (input layer IV)
5. Alignment of neuronal excitability with acoustic structure
Temporally organized spike train (output layers II/III)
High excitability
Strong spiking
Low excitability
1. Phase reset
4. Modulation of neuronal excitability and output discretization
Stimulus-induced theta-modulated gamma oscillations (25–35 Hz)
3. Theta/gamma nesting
Stimulus-induced theta oscillations (1–8 Hz; LFP, EEG, MEG)
2. Stimulus envelope tracking

FIGURE 26.2. Proposedoscillation-basedoperationsinspeechperception.Asequenceofoperations allows connected speech to be segmented by cortical theta and gamma oscillations. A high-resolution spectrotemporal representation of speech in primary auditory cortex is assumed. A typical afferent spike train activates layer IV cortical neurons. Many of these neurons phase-lock to speech amplitude modulations. Response onset elicit theta oscillations reset in superficial layers (step 1), where auditory cortex output is generated. By way of phase reset, theta oscillations track the speech envelope (step 2). Theta reset induces a transient break in gamma activity and a subsequent reset of gamma oscillations. Theta and gamma generators, weakly coupled at rest, become more strongly coupled and nested (step 3). Gamma power, in turn, controls the excitability of neurons generating the feedforward signal from A1 to higher order areas (step 4). Neuronal excitability phase now aligns to speech modulations (step 5).

Ghitza (2011) has proposed a parallel phenomenological model (Tempo) in which auditory information is processed simultaneously along two paths: a parsing (or segmentation) path and a decoding path. The *parsing* path, in alignment with the Giraud and Poeppel model, is composed of an array of cascaded oscillators in which the theta oscillator serves as the master by providing syllabic level parsing. The theta oscillator sets the boundary conditions for higher-frequency oscillatory activity, which in turn is argued to regulate finer-grained within-syllable fragmentation and ultimately diphone-based, phoneme-based, or feature-based fractionation. The assumption in this model is that these oscillators can phase-lock to the rhythms of the input within a given range of frequencies. The output of these oscillators is fed to the *decoding* path, which performs fine-grained pattern recognition at the level of smaller speech units.

We first review some of the psychophysical evidence supporting the role of theta oscillations in syllabic parsing, as proposed by the models described in the preceding. Decomposing speech into spectral and temporal modulations reveals that most of the power of the signal is concentrated in the low frequency range (2–10 Hz) (Greenberg, 2006; Greenberg, Carvey, Hitchcock, & Chang, 2003; Houtgast & Steeneken, 1985). Psychophysical studies suggest that modulations in this low range are critical for speech intelligibility (Drullman, Festen, & Houtgast, 1996; Drullman, Festen, & Plomp, 1994a, 1994b; Ghitza, 2012; Ghitza et al., 2012).

Ghitza and Greenberg (2009) used a novel method to restore intelligibility of time-compressed speech. Speeding up speech by a factor of 3 or more severely impairs intelligibility; but, surprisingly, insertion of silent gaps in between successive intervals of the compressed speech can substantially improve intelligibility. By manipulating the duration of the silent gaps (while holding the length of the presented acoustic chunks constant at 40 ms), Ghitza and Greenberg (2009) showed that the relationship between intelligibility and silent gap duration has a U-shape, where intelligibility peaks for a gap of 80 ms long. These results are compatible with the Tempo model (Ghitza, 2011): at a compression rate of 3, the theta oscillator hits its boundary and can no longer track speech, and therefore intelligibility is impaired. The insertion of silent gaps is interpreted as a repackaging of the speech signal in a way that allows the (syllable-sized) theta oscillator to once again lock again to the input rhythm, allowing parsing and therefore decoding.

In a later study, Ghitza (2012) examined the intelligibility of speech using a manipulated modulation spectrum. Two classes of stimuli were synthesized: one class carried acoustic-phonetic information sufficient for the function of the decoding path (as per the Tempo model) but lacked the input syllabic rhythm (needed for the operation of the parsing mechanism of the Tempo model). This was achieved by filtering out 2–9 Hz modulation information from speech, thus flattening the temporal envelope of the signal. As expected, the intelligibility of this class of stimuli was low. The second class of stimuli was generated by adding to the first stimulus type a signal that carried information restricted to the input rhythm alone (i.e., without any acoustic-phonetic content). This was achieved by placing clicks at the mid-vowel locations (that were eliminated by the original filtering). This surprisingly simple manipulation resulted in significant improvement in intelligibility. In other words, reinstating the input *rhythm* with an auditory cue is argued to restore theta-based parsing, thus allowing the decoding path to extract information from the flat modulation spectrum.

In the first MEG study that addressed the relationship between phase patterns of neural responses and speech perception (Luo & Poeppel, 2007), participants were asked to listen to naturally spoken sentences. An inter-trial coherence analysis revealed that the phase, but not the power, of theta-band (4–8 Hz) oscillations tracks the dynamics of speech and supports the reliable discrimination of different sentences. In a later study (Luo, Liu, & Poeppel, 2010), these findings were extended to the multi-modal case. In this study, participants were presented with short audiovisual movie clips while MEG responses were recorded from auditory and visual cortices. Low-frequency (delta and theta) phase patterns in early visual and auditory cortices were shown to track naturalistic visual and auditory stimuli, respectively. In addition, the low-frequency phase pattern in one modality could track, to some extent, the stimulus structure of the other modality.

To what extent does theta-phase tracking reflect speech intelligibility? According to the models described here, tracking via entrainment of neural theta oscillations provides syllabic level parsing that is crucial for subsequent proper decoding of speech. In the original Luo and Poeppel study (2007), discriminability between different speech tokens was much lower for acoustically degraded sentences, which are also less intelligible, suggesting that theta phase is linked directly to speech intelligibility. However, a later study (Howard & Poeppel, 2010) showed that theta phase allows equally strong discrimination between time-inverted sentences, which are unintelligible. This suggests that theta-phase tracking depends on acoustic features of the speech signal, not comprehension. Theta-based tracking—and therefore syllabic level segmentation—might be necessary for comprehension but is clearly not sufficient.

A neurophysiological study examined the link between theta-phase tracking and intelligibility in a more direct way (Peelle et al., 2013). These authors varied the intelligibility of sentences using a noise-vocoding technique. Specifically, the number of frequency channels used in vocoding was manipulated, thus affecting intelligibility level while preserving the overall amplitude envelope. Even in the case of completely unintelligible speech, bilateral low-frequency MEG responses were phase-locked to the envelope of the auditory signal. However, phase-locking was *enhanced* for intelligible speech, especially in left temporal cortex. The authors further showed that this result cannot be attributed to changes in spectral complexity. This was done by comparing responses with four-channel-vocoded speech (partially intelligible) to spectrally rotated four-channel-vocoded speech (unintelligible). Even when spectral complexity was held constant, phase-locking was stronger for intelligible speech. Thus, these results demonstrate that phase-locking is not driven solely by acoustic factors.

So far, we have focused on theta phase-locking. As proposed by the models described at the beginning of this section, speech perception is governed by a hierarchy of oscillators in which the theta oscillator is the master (Ghitza, 2011; Giraud & Poeppel, 2012). This conjecture is based on findings in both human and nonhuman primates showing that the phase of theta (4–8 Hz) oscillations can determine the amplitude of gamma (30–90 Hz) oscillations via a mechanism called phase-amplitude coupling (Canolty et al., 2006; Canolty & Knight, 2010; Lakatos et al., 2005). Are cortical oscillations hierarchically coupled during speech perception? A recent study used MEG and information theory to shed light on that important issue (Gross et al., 2013). Participants listened to a 7-minute long audio story, as well as its backward version. The authors used mutual information to assess the dependencies between the speech signal and cortical oscillations. As demonstrated by previous studies (Cogan & Poeppel, 2011), it was found that low-frequency speech modulations entrain delta and theta oscillations in auditory cortex. Importantly, it was also shown that low-frequency *phase* is coupled to the *amplitude* of broadband cortical gamma (Gross et al., 2013). It was demonstrated that speech tracking (theta-band phase-locking) as well as cross-frequency coupling were enhanced following temporal edges in speech. These effects outlasted the typical evoked response to edge onset (Gross et al., 2013).

The role of acoustic edges in speech entrainment has been the focus of another recent investigation (Doelling, Arnal, Ghitza, & Poeppel, 2014). This study used the stimulus set developed by Ghitza (2012) that was described earlier. Recall that Ghitza (2012) showed that reinstating temporal cues by using transient edges (e.g., clicks) at landmark positions (e.g., "missing" vowel peaks due to filtering procedures) enhanced intelligibility. Doelling et al. (2014) illuminated the neural basis of this psychophysical effect by showing that adding temporal cues to the filtered stimuli improves speech tracking. Moreover, there was a robust correlation between speech tracking and intelligibility. Taken together these findings suggest (1) that sharp fluctuations in the speech signal (e.g., edges) allow slow oscillations in auditory cortex to entrain, and (2) that this entrainment is necessary (although not sufficient) for speech comprehension.

There is accumulating evidence supporting the notion that cortical oscillations provide a way to temporally organize the incoming connected speech signal. In accordance with theoretical models (Ghitza, 2011; Giraud & Poeppel, 2012), psychophysical and neural evidence suggests that theta-band oscillations track the envelope of speech and provide a means for syllabic-based parsing. Theta-tracking of speech is likely driven by acoustic features (such as edges), but nonetheless it also reflects speech intelligibility. Recent studies also support the hypothesis that cortical oscillations are organized hierarchically, such that the phase of lower-frequency oscillations is coupled to the amplitude of broadband gamma oscillations. That coupling might provide a mechanism to align neural excitability with speech modulations.

What is the appeal of bringing neuronal oscillations to the domain of speech perception? One compelling argument is that oscillations form part of a linking hypothesis between the physics of speech, phonological attributes of speech, and the neurophysiological foundations of speech perception. When analyzing, cross-linguistically, the physical amplitude modulations of speech (i.e. what arrives at the ear), there is remarkable consistency: the modulation spectrum peaks between 4 and 5 Hz (Ding et al., 2017). This physical attribute of the speech signal, very robust, is actually what neural oscillations can "lock" onto, specifically when one speaks of phase-locking. The large amplitude fluctuations provide a physics-based scaffolding to which the neurophysiological machinery can connect. And it is no accident that it is theta band oscillations, between 4 and 8 Hz, that are precisely the physiological mechanisms linking to the physical signal. The third component of this linking hypothesis is that the mean duration of syllables, across languages, is between 150 and 300 ms. Therefore, from the point of view of language, as well, the same time scale is foundational. In summary, syllable duration (from linguistics), the modulation spectrum (from physics), and low-frequency brain rhythms (from neuroscience) provide the infrastructure for a plausible theory of speech segmentation.

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CHAPTER 27

SENTENCE PROCESSING

Toward a Neurobiological Approach

INA BORNKESSEL-SCHLESEWSKY
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Introduction: Neurolinguistics Meets Neurobiology

The past two decades have seen major changes in the neurolinguistic perspective on sentence processing. Following an earlier shift, in which "neurolinguistic" research broadened beyond its original focus on patient studies, more recent efforts have attempted to move the field toward a neurobiologically plausible perspective. Accordingly, neurolinguistic models of sentence processing must go beyond traditional cognitive approaches, and instead take into account how mechanisms of language processing are implemented by the brain (Rösler, 2011; Small, 2008). This is a challenging enterprise: language is notoriously difficult to study from a biological perspective, since—prima facie—it defies analysis based on detailed animal models. The challenge is heightened even further when considering the sentence level, with its complex combinatory meanings.

A true neurobiology of sentence processing thus currently lies beyond our achievable grasp. Nevertheless, substantial progress has been made in moving toward a perspective that is informed by biological design principles and insights from basic neuroscience. Notable developments include the following:

- *Language—including sentence processing—as embedded within the broader perception-action cycle implemented by the brain.* As articulated perhaps most clearly by motor neuroscientist Daniel Wolpert and his colleagues, the purpose of the human brain is to allow us to effectively interact with the world around us. In their words, which they explicitly characterize as "a motor chauvinist's point of view": "the entire purpose of the human brain is to produce movement" (Wolpert, Ghahramani, & Flanagan, 2001, p. 487). At first glance, this perspective may appear odd when applied to language. However, as we discuss in more detail later in this chapter, sensorimotor integration and the brain circuits that perform it have played a major role in advancing theories of sentence processing toward a more biologically informed perspective.

- *A move away from abstract representations*. In accordance with the observation that any neurobiologically plausible theory of language must be embedded in a holistic theory of brain function, there is a clear trend away from viewing the generation of abstract representations as the be-all and end-all of language processing (and particularly language comprehension) in the brain. The degree to which abstract representations—for example, an abstract conceptual representation of sentence meaning—are needed, what they might look like, and how they are represented/processed by the brain remains a matter of vigorous debate (see Meteyard, Cuadrado, Bahrami, & Vigliocco, 2012, for a review). Nevertheless, many researchers in the field would agree that the purpose of such representations—whatever their level of embodiment or abstraction—is to inform appropriate action.
- *Dual-stream anatomical models of language processing*. In accordance with the general recognition in cognitive neuroscience that brain networks, rather than isolated regions, provide an appropriate level at which to study cognitive functions, there is now a strong consensus that language processing in the brain must be studied at the systems level, taking into account anatomical and functional connectivity (Behrens & Sporns, 2012). For language—including sentence—processing, dual-stream anatomical models are now widely recognized (Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015a; Friederici, 2011; Hagoort, 2014; Hickok & Poeppel, 2007; Rauschecker, 1998; Rauschecker & Scott, 2009; see also Hickok, Chapter 20 in this volume). However, the various accounts make different claims about the nature of the computational mechanisms performed by the dual streams and the division of labor between streams (see also Skipper, Devlin, & Lametti, 2017, for a critical view).

In the following, we first outline the anatomical foundations of current dual-stream models of sentence processing, before turning to candidate computational mechanisms for sentence processing in the brain. We then discuss the current state of knowledge in regard to the time course of sentence processing in the brain, before offering some brief conclusions and providing an outlook.

ANATOMICAL FOUNDATIONS

There is now a broad consensus that sentence processing draws upon dual cortical streams of information processing (Bornkessel-Schlesewsky & Schlesewsky, 2013;

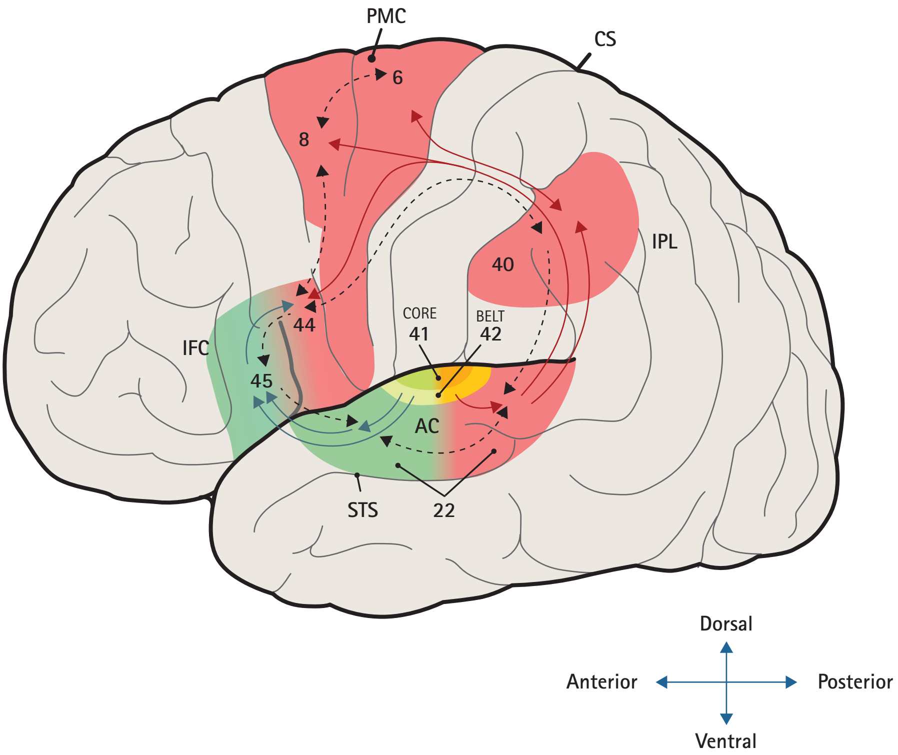

FIGURE 27.1. Schematic illustration of the dorsal (red) and ventral (green) speech- and language-processing streams Numbers denote Brodmann areas and arrows depict anatomical connectivity (black dashed arrows denote feedback connections).

Abbreviations: AC = auditory cortex; CS = central sulcus; IFC = inferior frontal cortex; IPL = inferior parietal lobule; PMC = premotor cortex; STS = superior temporal sulcus.

Source: Reproduced, with permission, from Bornkessel-Schlesewsky et al. (2015a).

Bornkessel-Schlesewsky et al., 2015a; Friederici, 2009, 2011, 2012; Hagoort, 2014), building on models of nonhuman primate audition (Rauschecker, 1998; Rauschecker & Tian, 2000) and human speech processing (Hickok & Poeppel, 2000, 2004, 2007; Rauschecker & Scott, 2009; see, in this volume, Peelle, Chapter 13, and Poeppel, Cogan, Davidesco, & Flinker, Chapter 26). The (postero-)dorsal and (antero-)ventral streams (see Figure 27.1) both serve to connect the auditory cortex (AC) in the superior temporal lobe with the prefrontal cortex, showing clear homologies to the nonhuman primate brain (for further anatomical details, see Catani & Forkel, Chapter 9 in this volume).

In nonhuman primates, the ventral and dorsal streams have been associated with auditory object recognition and spatial auditory processing, respectively (Rauschecker, 1998; Rauschecker & Tian, 2000; Rauschecker, Tian, & Hauser, 1995). The ventral stream shows a hierarchical organization, with lower levels (more proximate to core regions of AC) tuned to basic auditory features (e.g., frequency-modulated [FM] sweeps, band-pass noise bursts) and higher levels tuned to complex spectrotemporal patterns via sensitivity to a combination of lower-level features (Kikuchi, Horwitz, & Mishkin, 2010; Rauschecker et al., 1995). Such patterns can be associated with specific meanings, for example in species-specific vocalizations ("monkey calls") (see Rauschecker & Scott, 2009, for detailed discussion). Recent neuroimaging evidence in humans suggests a comparable hierarchical organization of the dorsal stream, with higher levels displaying temporal integration windows of increasing length (Hasson, Chen, & Honey, 2015; Lerner, Honey, Silbert, & Hasson, 2011; for sentence processing, see also Bornkessel-Schlesewsky & Schlesewsky, 2013; Bornkessel-Schlesewsky et al., 2015a).

ANATOMICAL MODELS OF THE NEUROBIOLOGY OF SENTENCE PROCESSING AND CANDIDATE COMPUTATIONAL MECHANISMS

Beyond the acknowledgment of a dorsal-ventral division of labor, there is currently no consensus regarding the function that each stream performs in sentence processing. There are several competing accounts, as outlined in the following. We will first consider general accounts of dorsal and ventral stream functionality in speech and language, before turning to proposals that focus specifically on mechanisms of sentence processing

Extrapolation from Speech Processing

By building on insights on the primate auditory system, dual-stream models of speech processing constitute an important first step in moving toward neurobiologically plausible models of speech and language. They thus provide a crucial basis for neurobiological models of sentence processing.

The model by Rauschecker and Scott (2009) is grounded in the functions of the dual streams in nonhuman primate audition: auditory object recognition in the ventral stream (Rauschecker, 1998; Rauschecker & Tian, 2000; Rauschecker et al., 1995; for a recent review of auditory object processing, see Bizley & Cohen, 2013), and auditory spatial processing in the dorsal stream (Rauschecker & Tian, 2000; see Rauschecker, 2011, for a review). The relevance of auditory object processing for speech and language perception appears straightforward: units such as phonemes, words, and phrases constitute linguistic auditory objects, and hence their perception plausibly draws on similar mechanisms as the perception of auditory objects in nonhuman primate audition (see earlier discussion). Indeed, auditory object recognition in nonhuman primates shares important characteristics with human speech processing, such as categorical perception and categorization into abstract, meaning-based units (Tsunada, Lee, & Cohen, 2011, 2012). As in auditory object recognition, the ventral stream shows hierarchical organization in speech perception (DeWitt & Rauschecker, 2012), and plays an important role in the sound-to-meaning mapping (Saur et al., 2008; Scott, Blank, Rosen, & Wise, 2000). Further converging evidence for the ventral stream's role in conceptual processing in humans stems from the deficits shown by patients suffering from the semantic variant of primary progressive aphasia, which involves atrophy of the anterior temporal lobes (e.g., Gorno-Tempini et al., 2011; Mesulam, Grossman, Hillis, Kertesz, & Weintraub, 2003), as well as from neuroimaging (see Visser, Jefferies, & Lambon Ralph, 2010, for a recent meta-analysis), transcranial magnetic stimulation (Chiou, Sowman, Etchell, & Rich, 2014; Pobric, Jefferies, & Lambon Ralph, 2007; see Schuhmann, Chapter 5 in this volume), and computational modeling (Ueno, Saito, Rogers, & Lambon Ralph, 2011).

The spatial function of the dorsal stream, by contrast, seems less readily associable with speech- and language-related functions at first glance. As suggested by Rauschecker and Scott (2009) and Rauschecker (2011), internal (forward and inverse) models may provide a common computational denominator between the dorsal stream's spatial and speech-related functions. First posited for motor control (Wolpert, Ghahramani, & Jordan, 1995) and extended to neural models of the body and the environment (Grush, 2004), internal models are now assumed in a wide range of areas in cognitive neuroscience (e.g., to account for one's sense of agency: Blakemore, Wolpert, & Frith, 1998; theory of mind: Koster-Hale & Saxe, 2013; language processing: Pickering & Garrod, 2007, 2013; audiovisual integration during speech processing: van Wassenhove, Grant, & Poeppel, 2005; and social interactions: Wolpert, Doya, & Kawato, 2003). They are well suited to explaining rapid state transitions in the world, such as the sensory consequences of actions. According to Rauschecker and Scott (2009, p. 722), "spatial transformations may be one example of fast adaptations used by 'internal models,' " thus explaining the commonality between the spatial function of the dorsal stream and its role in auditory-motor mappings (mapping sounds to articulations; see Tremblay, Deschamps, & Dick, Chapter 15 in this volume).

The assumed auditory-motor function of the dorsal stream also plays a central role in the prominent dual-stream model of speech perception developed by Hickok and Poeppel (2000, 2004, 2007; see also Hickok, Chapter 20 in this volume). In their approach, the auditory-motor integrations performed by the dorsal stream render it important for speech production, as well as for language learning (acquiring these mappings). The ventral stream, by contrast, is crucial for speech perception, via its previously mentioned involvement in mapping sound to meaning. Prima facie, Hickok and Poeppel's approach is thus highly similar to Rauschecker and Scott's (2009) proposal with respect to the function of the dual auditory streams. There are, however, at least three important differences between the two models. First, Hickok and Poeppel's assumptions about the anatomy of the streams is motivated functionally (i.e., by neuroimaging evidence in humans), rather than based on anatomical insights from nonhuman primates. Thus, the assumed mapping between cortical regions and streams differs from that assumed by Rauscher and Scott: following an initial, unified cortical stage of speech processing in AC and the middle and posterior superior temporal sulcus (STS), the ventral stream projects via posterior middle and inferior temporal cortex (deemed the *lexical interface* that maps sound onto meaning) to the anterior temporal lobe (deemed the *combinatorial network*, which allows for a predictable meaning to emerge when smaller linguistic units are combined into larger ones). The dorsal stream, by contrast, projects via the temporo-parietal junction and a region located there (area Spt, an assumed sensorimotor interface) to posterior inferior frontal and premotor regions (the articulatory network). The second substantive difference between the Hickok and Poeppel model, on the one hand, and the Rauschecker and Scott model, on the other, concerns the role of the dorsal stream, which is primarily conceived of as auditory-motor mapping by Hickok and Poeppel (in contrast to Rauschecker and Scott's broader functional view; see earlier discussion). Third, Hickok and Poeppel's model focuses more strongly on hemispheric asymmetries between the two streams, positing a bilateral organization of the ventral stream, while the dorsal stream is strongly left-lateralized.

Clearly, the functional and anatomical assumptions made by current neurobiological models of speech processing are also potentially relevant for neurobiological models of sentence processing. However, they do not provide a mechanistic account of sentence processing in the brain, that is, they do not explain the neurobiological mechanisms by which the brain combines words and morphemes to form sentences and how it supports the complex form-to-meaning mapping at this level. Accordingly, several neurobiological models have been proposed that directly address language processing at the sentence level (and beyond, in some cases). These will be the focus of the following subsections.

The Auditory Sentence Comprehension Model

One of the first dual-streams models to make specific assumptions about sentence-level processing was proposed by Friederici (2009), and was elaborated upon in subsequent publications (Friederici, 2011, 2012). This model of auditory sentence comprehension posits an additional structural-functional layer that complements the assumptions of the previously mentioned speech-processing models. In other words, Friederici assumes that the dorsal and ventral streams both comprise multiple anatomical subpathways with dissociable functions. Let us turn first to the dorsal stream. In addition to its role in auditory-motor mappings, it fulfills the second function of processing complex syntactic structures in Friederici's model. However, while auditory-motor integration is thought to be subserved by a projection from posterior superior temporal (pST) regions to the inferior parietal lobule (IPL) and premotor cortex (PMC) via the superior longitudinal fasciculus (SLF), complex syntax processing draws upon direct temporo-frontal connectivity from pST cortex to the *pars opercularis* (POp) of the left inferior frontal gyrus (BA 44) via the arcuate fasciculus (AF). Similarly, the ventral stream is assumed to support not only sound-to-meaning mappings (via the extreme capsule, EC), but also the processing of simple syntactic information (via the uncinate fasciculus, UF) (for further details, see Friederici, 2012).

The dissociation between simple and complex syntax is central to Friederici's approach and thus requires some elaboration. She uses simple syntax to refer to the local (i.e., essentially phrase-internal) combination of word categories (e.g., determiners and nouns to form a noun phrase such as "the bridge," or prepositions and noun phrases to form a prepositional phrase such as "under the bridge"). Mechanisms of complex syntax processing, by contrast, are required in the case of word order permutations (e.g., object-initial sentences in languages that allow them) and self-embeddings (i.e., recursion, for example in sentences including relative clauses).

Evidence for involvement of the dorsal stream in complex syntax processing stems from neuroimaging studies showing increased, mostly left-lateralized activation of the posterior superior temporal sulcus and/or gyrus (pSTS/STG) and of the POp for object- versus subject-initial sentences (e.g., Ben-Shachar, Palti, & Grodzinsky, 2004; Bornkessel, Zysset, Friederici, von Cramon, & Schlesewsky, 2005; Burholt Kristensen, Engberg-Pedersen, Højlund Nielsen, & Wallentin, 2013; Christensen & Wallentin, 2011; Fiebach, Schlesewsky, Lohmann, von Cramon, & Friederici, 2005; Friederici et al., 2006; Kinno, Kawamura, Shioda, & Sakai, 2008; Röder, Stock, Neville, Bien, & Rösler, 2002) and sentences with increasing depths of self-embedding (Makuuchi, Bahlmann, Anwander, & Friederici, 2009). The results by Makuuchi and colleagues were additionally interpreted as dissociating the processing of hierarchical structures—as required in self-embeddings—from working memory requirements (implemented via the insertion of linear dependencies without any embedded clauses; see Buchsbaum, Chapter 32 in this volume). While embedded (hierarchical) dependency processing engendered increased activation in the POp, linear dependency processing correlated with an anatomically separable activation increase in the inferior frontal sulcus (IFS). Within the dorsal sub-pathway that engages in the processing of complex syntax, Friederici envisages the division of labor among regions as follows: "BA 44 is the core region of syntactic processes across different languages (Friederici, 2011) and tasks (Caplan, Chen, & Waters, 2008), whereas the posterior temporal region comes into play when argument assignment in the service of sentence interpretation is required (Bornkessel et al., 2005; Hickok & Poeppel, 2007; Kuperberg et al., 2000; Newman, Ikuta, & Burns, 2010; Snijders et al., 2009)" (Friederici, 2012, p. 265).

The claim that complex syntax processing is specifically tied to a direct dorsal sub-pathway that connects pST to the POp stems mainly from Friederici and colleagues' work on language acquisition. Diffusion tensor imaging (DTI; see Catani & Forkel, Chapter 9 in this volume) suggests that this dorsal sub-pathway, which is deemed responsible for complex syntax, is not present at birth and matures slowly (Perani et al., 2011). This contrasts with ventral fiber tracts and the second dorsal sub-pathway, which is deemed to be responsible for auditory-motor mapping. Consequently, until the direct dorsal sub-pathway is fully matured—which Friederici and colleagues assume is not the case until after 7 years of age—children are unable to process object-initial word orders very accurately (cf. Dittmar, Abbot-Smith, Lieven, & Tomasello, 2008) and show (accuracy-dependent) inferior frontal activation differences from adults during the processing of word-order variations (Knoll, Obleser, Schipke, Friederici, & Brauer, 2012).

Younger children are therefore thought to rely more strongly on the ventral pathway during sentence processing (Brauer, Anwander, & Friederici, 2011). A similar claim has been made for elderly adults, based on functional magnetic resonance imaging (fMRI) and DTI findings from sentences involving embeddings (Antonenko et al., 2013).

The Memory, Unification, and Control Model

In his neurocognitive model of language, Hagoort conceives of sentence processing as supported by three general computational components: memory, unification, and control (MUC; Hagoort, 2005). The memory and unification components subserve the storage of linguistic information in long-term memory and its combination into more complex units, respectively. They thus correspond roughly to the assumed dissociation between lexicon and grammar in linguistics (Chomsky, 1965), or between an associative memory system and a rule-based computational component in cognitive science (Pinker, 2009). Note, however, that Hagoort subscribes to a lexicalist grammar (cf. MacDonald, Pearlmutter, & Seidenberg, 1994; Vosse & Kempen, 2000) and thus assumes that syntactic structures are associated with lexical items and stored in memory as templates. Structure building therefore involves the combination ("unification") of these templates to form larger structures and is not directly compatible with Chomskyan notions of grammar. The third (control) component of the MUC architecture performs a regulatory role and thus corresponds to the notion of executive functions in cognitive psychology (see Baddeley, 2012, for a review) or cognitive control in cognitive neuroscience (e.g., Kimberg & Farah, 1993; Miller & Cohen, 2001; for cognitive control and language processing, see Novick, Trueswell, & Thompson-Schill, 2005; Thompson-Schill, Bedny, & Goldberg, 2005; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). According to the MUC model, the memory component is associated with the left posterior temporal lobe (cf. Hickok and Poeppel's assumption of posterior temporal areas as a lexical interface) and adjacent inferior parietal regions (Hagoort, 2013, 2014). The left inferior frontal gyrus (IFG), by contrast, is envisaged as the neural "unification space." It is organized along a unification gradient from antero-ventral to postero-dorsal parts of the left IFG, with semantic unification associated with the *pars orbitalis* (POr) and *pars triangularis* (PTr) (BA 47/45), syntactic unification with the PTr and POp, and phonological unification with the POp and adjacent ventral PMC. In some sense, the MUC model is thus in agreement with Friederici's (2012) assumption that the POp should be viewed as the core syntax region in the brain. However, it contrasts with Friederici's model in assuming a lexicalist view of syntax as described in the preceding and in viewing syntactic unification as only one of the various types of unification performed by the left IFG. Finally, control is thought to engage parts of dorsolateral prefrontal cortex (DLPFC), as well as the anterior cingulate cortex (ACC) and attention-related parietal regions.

The MUC model has not, to date, made any strong claims about a separable functional significance of the dorsal and ventral streams for language processing, beyond their dual role in connecting the memory- and unification-related nodes of the overall language network. However, based on functional connectivity measures obtained from resting-state fMRI (Xiang, Fonteijn, Norris, & Hagoort, 2010), Hagoort (2013) recently argued that phonological, syntactic, and semantic processes show dissociable connectivity patterns within the overall language network. Though these functional patterns are orthogonal to—and, in the case of Xiang et al.'s (2010) findings, do not straightforwardly correspond to—anatomical connectivity, Hagoort concludes from these data that "[t]he dorsal pathways might be most relevant for phonological and syntactic processing, while the ventral pathways seem to be strongly, but presumably not exclusively, involved in connecting regions for semantic processing" (Hagoort, 2013, p. 4).

Key evidence in favor of the MUC's signature division of labor between its temporal memory component and its inferior frontal unification component stems from an fMRI study by Snijders et al. (2009). These authors investigated the processing of category-ambiguous words (i.e., words that can be used as a noun or a verb), either as part of a word list or in a sentence context. While the left posterior middle temporal gyrus (pMTG) showed increased activation for ambiguous versus unambiguous words in word lists and sentences, the left IFG showed an ambiguity effect only for sentences. This was viewed as evidence for the lexical role of the pMTG due to the ambiguity effect observed at the word level, and for a role of the IFG in combinatorics, due to the ambiguity effect requiring a sentence context (i.e., multiple unification options, in Hagoort's terminology). In support of the assumed unification gradient between syntactic and semantic information, Hagoort and Indefrey (2014) report a meta-analysis of over 100 neuroimaging (fMRI and PET) studies, which involved a manipulation of syntactic and/or semantic processing demands at the sentence level. The results of this study suggested that syntactic processing difficulty led to a reliable activation of BA 44/45, while semantic processing difficulty was more typically associated with activation of BA 45/47. A similar gradient was observed for the posterior temporal lobe.

A final hallmark of the MUC is that it explicitly acknowledges the need to understand how the neurobiology of language processing interacts with broader brain systems, such as those involved in attention (see the earlier discussion of the control component) and theory of mind (Hagoort, 2013). The MUC thereby aims to provide a neurobiological framework for sentence processing as embedded in a broader discourse and in relation pragmatic demands.

The Bi-hemispheric Model

Tyler and Marslen-Wilson's bi-hemispheric model of language comprehension is based on the assumption of two separable brain systems for sentence processing: a left-lateralized fronto-temporal system for syntactic processing, and a bilateral temporo-parietal system for semantic/pragmatic processing (Tyler & Marslen-Wilson, 2008). Thus, like the approaches by Friederici and Hagoort, this model posits that traditional linguistic subdomains such as syntax, semantics, and phonology provide appropriate levels of representation for characterizing the neurobiology of language. It differs from these, however, in its characterization of the circuits involved in the processing of each information type, as well as in its stronger focus on hemispheric asymmetries.

Early characterizations of the bi-hemispheric model emphasized the separability of syntactic and semantic information processing within the broad perisylvian language network (Tyler & Marslen-Wilson, 2008). Based primarily on studies of syntactic and semantic ambiguity processing at the sentence level (Rodd, Longe, Randall, & Tyler, 2010), semantic processing was assumed to correlate with activation in left lateral inferior frontal and left anterior superior temporal regions, while syntactic processing engaged both of these regions, as well as pST and inferior parietal areas. The dissociability of these networks was supported by functional connectivity analyses. In addition, only activations in response to syntactic ambiguity (a word category ambiguity, as in "he noticed that *landing planes* **frightens/frighten** some new pilots"; ambiguous region in italics, disambiguating region in bold) were modulated by dominance (i.e., the degree to which one reading is preferred over the other). By contrast, activations in response to semantic ambiguities (homonyms, as in "in Australia, strange *barks* **grow** on many trees") were unaffected by dominance. From these findings, Tyler and Marslen-Wilson concluded that semantic and syntactic processing is accomplished by separable fronto-temporal systems, which differ not only with regard to the regions involved and their connectivity, but also mechanistically (i.e., while syntactic processing appears to be preference-driven, such that the dominant reading is adopted quickly and incrementally, semantic processing appears to sustain multiple readings until disambiguating information is encountered). With reference to their extensive previous work on morphological processing, Tyler and Marslen-Wilson (2008) additionally argued that the network for syntactic processing is more strongly comparable to that observed for the processing of regular inflectional morphology (or phonological information resembling regular inflectional morphemes), rather than to the network for semantic processing. Nevertheless, the syntactic and morphological networks do not appear to be identical, as suggested by separable loci within the pMTG identified via functional connectivity analyses seeded in the left IFG. Evidence for the left lateralization of the networks for morphological/syntactic processing and stronger bilaterality of the network for semantic processing stems mainly from patient studies, with patients with left-hemispheric, perisylvian lesions able to show normal performance on semantic tasks (accompanied by increased recruitment of right-hemispheric regions), but not on syntactic or morphological processing tasks.

Subsequent work within the scope of the bi-hemispheric model further fleshed out the assumed contribution of dorsal and ventral fiber tracts to the picture outlined in the preceding. Rolheiser, Stamatakis, and Tyler (2011) examined chronic stroke patients using DTI and employed a battery of tests designed to measure phonological, morphological, syntactic, and semantic processing. All patients had left-hemispheric lesions, but these differed in location and extent. Voxel-by-voxel correlations between white matter integrity and behavioral performance suggested that semantic and phonological processing relied on ventral and dorsal fiber systems, respectively, while morphological and syntactic processing correlated with both streams. In another patient study (Papoutsi, Stamatakis, Griffiths, Marslen-Wilson, & Tyler, 2011), effective connectivity between the left IFG and the left pMTG was shown to correlate with syntactic processing performance. From these results, the authors concluded that a division of labor between the dorsal and ventral streams only holds for phonology versus semantics, while morphology and syntax draw on both streams.

In summary, the bi-hemispheric model resembles the MUC model in emphasizing the importance of a network comprising the left IFG and left pMTG for syntactic processing, with the left pMTG engaged in lexical processing, and the left IFG responsible for sentence-level processes such as ambiguity resolution (for recent supporting evidence from multivariate pattern analysis, see Tyler, Cheung, Devereux, & Clarke, 2013).

The Extended Argument Dependency Model

The (extended) Argument Dependency Model (eADM) was originally conceived as a neurocognitive model of sentence processing that aspired toward cross-linguistic plausibility (Bornkessel, 2002; Bornkessel & Schlesewsky, 2006; Schlesewsky & Bornkessel, 2004). In other words, the aim of the model was to account for the similarities and differences in sentence processing across the world's 7,000 languages, both from a cognitive and from a brain-based perspective. More recent versions of the model have focused more strongly on a neurobiological grounding, based on a dual-stream architecture (Bornkessel-Schlesewsky & Schlesewsky, 2013; Bornkessel-Schlesewsky et al., 2015a). In its most recent instantiation as a neurobiological model of sentence processing, the eADM differs from the models described in the preceding subsections in at least two important respects:

- *Neurobiological grounding of language in primate audition*. The most recent versions of the eADM posit that higher-order language processing can be grounded in basic computational mechanisms that are already evident in (nonhuman) primate audition. In essence, this amounts to the claim that the step from nonhuman primate audition to human language is quantitative, rather than qualitative. This assumption is in direct disagreement with Friederici's (2011, 2012) auditory sentence comprehension model, both anatomically and functionally. In anatomical terms, Friederici and colleagues argue that the direct dorsal pathway from pST to the POp via the AF is not present in monkeys (based on work by Rilling et al., 2008) and, as described earlier, matures slowly in children. The eADM, by contrast, questions the validity of this conclusion based on anatomical tracer studies in monkeys (Frey et al., 2014; Romanski et al., 1999; for discussion, see Bornkessel-Schlesewsky, Schlesewsky, Small, & Rauschecker, 2015b). Functionally, the eADM posits that nonhuman primates *are*, in principle, able to process hierarchically structured sequences, but at a lower level of sophistication (i.e., hierarchical depth) than humans (Bornkessel-Schlesewsky et al., 2015a).

- *Basic information-processing mechanisms rather than linguistic subdomains.* In contrast to all of the models discussed in the preceding subsections, the eADM does *not* assume that traditional linguistic subdomains such as syntax and semantics provide an adequate level of description for how sentences are represented in and processed by the brain. Rather, the model focuses on basic mechanisms of information processing inspired by cross-linguistic research. Specifically, it posits that both the dorsal and ventral streams are crucial for combining linguistic units into more complex units (e.g., words and morphemes into sentences), but that the two streams differ in the nature of the combinatoric operations that they support (see later in the chapter for further details).

The signature claim of the eADM is that the mechanisms supporting higher-order language combinatorics are grounded in the computational properties of the dual auditory streams: (1) an antero-ventral stream that recognizes successively more complex (feature-rich) auditory objects and thereby performs a mapping between spectrotemporal (auditory) input patterns and conceptual representations; and (2) a postero-dorsal stream that performs sequence processing at multiple levels based on a hierarchically organized predictive coding architecture. Both mechanisms are congruent with findings on (nonhuman) primate audition and the speech-processing model by Rauschecker and Scott (2009). Prefrontal cortex subserves both a regulatory function (Thompson-Schill et al., 2005) and integrates the information processed by the two streams.

In this framework, the *dorsal stream* performs *sequence-based, non-commutative* combinatorics (i.e., AB ≠ BA). This type of combinatorics corresponds to the necessity of keeping track of linear order during language comprehension, a property that is easily illustrated in English (i.e., the sentences "Tony helped Jim" and "Jim helped Tony" don't mean the same thing). The assumption that the dorsal stream plays an important role in sequencing is supported by results implicating the dorsal stream in the processing of word order (i.e., sentence-level sequencing; see the discussion of Friederici's model). Evidence from Primary Progressive Aphasia (PPA) patients further supports these claims: as shown by Wilson et al. (2011) using a sentence-picture-matching task, structural integrity of dorsal fiber tracts in these patients correlates with their ability to comprehend non-canonical[1] English sentences (in this study: passives such as "the boy is kicked by the girl"). Several further studies using voxel-based lesion-symptom mapping (VLSM; see Wilson, Chapter 2 in this volume) also observed a correlation between damage in dorsal stream regions in the posterior temporal and parietal lobes and impaired non-canonical (passive and object relative/cleft) sentence comprehension in English (Newhart et al., 2012; Thothathiri, Kimberg, & Schwartz, 2012). Importantly, the eADM maintains that findings such as these do not implicate the dorsal stream as a syntax stream per se, since the activations shown by the neuroimaging studies in question also rely on non-syntactic (e.g., semantic) sequencing parameters (Bornkessel et al., 2005; Bornkessel-Schlesewsky, Schlesewsky, & von Cramon, 2009; Grewe, et al, 2005, 2006). It also posits that the mechanism in question is one of sequence processing at multiple time scales, rather than of complex syntax processing, as dorsal stream regions are also implicated in the processing of sound sequences (e.g. Scott & Wise, 2004; Wise et al., 2001) and speech rhythm (Geiser, Zaehle, Jancke, & Meyer, 2008), as well as sequences at the discourse level (Kandylaki et al., 2016). A parsimonious explanation for these findings is that the dorsal stream processes sequence information in temporal receptive windows[2] of increasing length (Hasson et al., 2015; Lerner et al., 2011), thus demonstrating that, like the ventral stream, the dorsal stream is organized hierarchically (Bornkessel-Schlesewsky & Schlesewsky, 2013; Bornkessel-Schlesewsky et al., 2015a).

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[1] We use the term *non-canonical* to describe sentences that do not adhere to the typical agent-action-object template for English, as first described by Bever (1970).

The *ventral stream*, by contrast, is assumed to perform *non-sequence-based, commutative combinatorics* (i.e., AB = BA). This assumption is motivated by several observations. First, it builds on the observation that non-sequence-based interpretation is crucially important in many languages of the world, as illustrated aptly by example (1) from the Indigenous Australian language Jiwarli. The example includes a discontinuous noun phrase, with the demonstrative "this" which specifies "pipe of mine" occurring at the beginning of the sentence, while the remainder of the noun phrase is placed sentence-finally.

(1) Jiwarli, Pama-Nyungan, Western Australia (Austin, 2001)

Yinha	nhurra	parlura-rni-nma	payipa	nganaju.
this.acc	2sg.erg	full-caus-imper	pipe.acc	1sg.dat.acc

"You fill up this pipe of mine!"

At a first glance, sentences such as (1) may appear almost impossible to process—particularly from the perspective of a native speaker of English. However, flexible word order is a characteristic of many of the world's approximately 7,000 languages and, accordingly, there must be neural mechanisms available to process it. In this example, the noun phrase "this pipe of mine" can be identified as a constituent via case marking information, that is, all three words comprising the noun phrase bear accusative (acc) marking.[3] The eADM proposes that non-sequential information types, such as case marking, serve as grouping cues in the identification of linguistic auditory objects, in much the same way that acoustic cues such as harmonicity subserve the identification of non-linguistic auditory objects (Bizley & Cohen, 2013). Accordingly, the composition of larger linguistic units such as phrases—and likely even some highly frequent, templatic sentence forms—can be viewed as a more complex form of auditory object recognition.

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[2] Temporal receptive windows correspond to receptive fields in the visual system, but, as their name suggests, are defined in terms of time rather than space. They define the time scales within which auditory information is integrated (see also Poeppel, 2003).

[3] Note, however, that not all free word order languages have morphological case marking.

The eADM's conceptualization of the ventral stream thus provides a parsimonious explanation for this stream's involvement in conceptual processing (see earlier discussion) and in basic combinatorics (e.g., Bemis & Pylkkänen, 2011, 2013a; Brennan et al., 2012). The studies by Bemis and Pylkkänen demonstrate left aTL involvement in the composition of minimal phrases such as "red boat"; they further support the eADM's notion of commutative ventral stream combinatorics, by showing that—at least in the context of a task requiring compositional processing—left aTL activation is observable irrespective of noun-adjective order (i.e., for both "red boat" and "boat red"; Bemis & Pylkkänen, 2013b). Likewise, findings from semantic PPA patients indicate that aTL combinatorics are non-sequence-based: recall from the earlier discussion that these patients show pronounced anterior temporal lobe atrophy; nevertheless, they show a high accuracy in the comprehension of non-canonically ordered sentences such as passives (Wilson et al., 2014). This contrasts markedly with the previously mentioned result that PPA patients with damage to dorsal fiber tracts are impaired in their comprehension of such sentences (Wilson et al., 2011). Strikingly, recent VLSM results from Icelandic, a language with a rich case-marking system, showed that lesions in the left aTL correlated with deficits in the processing of non-canonically ordered sentences (passives, object clefts, and object wh-questions) (Magnusdottir et al., 2013; see also Kim, Jeon, & Lee, 2010, for similar results from Korean, another case-marking language). Taken together, the neuroimaging results and patient data support the eADM's view of commutative combinatorics in the ventral stream.

Extension to Reading

The reader will have noted that the discussion in the preceding subsections has focused almost exclusively on auditory sentence processing. At present, an extension of these insights to reading is—unfortunately—not possible. Though a number of neurobiological models of reading have been put forward (for recent discussions, see Carreiras, Armstrong, Perea, & Frost, 2014; Dehaene & Cohen, 2011; Price & Devlin, 2011; see also Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24 in this volume), our understanding of reading in the brain is currently limited to the word level. A challenge for future research thus lies in synthesizing insights on the neurobiology of visual word recognition with those on the neurobiology of sentence processing.

The Time Course of Sentence Processing in the Brain

Time course considerations have been the bread and butter of sentence processing theories for over three decades. They defined foundational debates in the field, such as the question of how and when different information sources are utilized during the comprehension of a sentence (modularity versus interactivity; see, e.g., Frazier, 1987; Frazier & Clifton, 1996; MacDonald et al., 1994; Rayner, Carlson, & Frazier, 1983; Trueswell & Tanenhaus, 1994). The advent of neurobiological models, however, has raised the question of how cognitive questions such as "is syntactic information initially prioritized over semantic information?" or "is information source X processed pre- or post-lexically (i.e., prior to or following lexical access)" can be framed in neurobiologically plausible terms (for discussion in relation to the time course of sentence processing, see Bornkessel-Schlesewsky, Staub, & Schlesewsky, 2016; for discussion of the notion of a mental lexicon, see Kutas & Federmeier, 2011).

Challenges to the development of a truly neurobiological perspective on the time course of sentence processing are manyfold. They include the following:

- *Difficulties in mapping cognitive and neural architectures onto one another*. In neurobiological terms, neither the strictly serial and encapsulated perspective of modular models nor the "everything is connected to everything" perspective of strongly interactive models (often with connectionist implementations) is plausible. Rather, neural streams of information processing (see earlier discussion) show a hierarchical organization, encompassing properties of both serial and parallel organization (Rauschecker & Scott, 2009). Ultimately, however, connectivity is considerably more complicated, involving both feedforward and feedback projections, and many, but not all connections are bidirectional (for detailed discussion in relation to the visual processing streams, see Kravitz, Saleem, Baker, & Mishkin, 2011; Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013). Moreover, hierarchical organization does not imply "serial" connectivity in the sense that a level *n* of the hierarchy is only connected to levels $n + 1$ and $n - 1$. Rather, long-range (feedforward and feedback) connections can "skip" individual levels of the hierarchy (for possible implications, see Bar, 2003).
- *Methods currently available to study the time course of language processing in the brain*. Electroencephalography (EEG; see Leckey & Federmeier, Chapter 3 in this volume) and Magnetoencephalography (MEG; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume) are typically used for this purpose in view of their exquisite temporal resolution. However, they provide rather macroscopic measures of brain activity. Functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume), by contrast, does not offer the temporal resolution required for the question under consideration. Electrocorticography (ECoG; i.e., the recording of electrophysiological activity directly from the cortex using subdural electrodes; see, e.g., Chang et al., 2010; Martin, Millán, Knight, & Pasley, in press, for applications to language), provides high resolution in both the temporal and the spatial domains. However, ECoG studies can only be performed with patients, and the electrode grids used typically only offer limited coverage as electrode placement is determined by clinical motivations.
- *Discrepancies between time course estimates obtained from neurophysiological and behavioral measures*. As has been observed repeatedly (e.g., Bornkessel &

Schlesewsky, 2006; Kretzschmar, Schlesewsky, & Staub, 2015; Rayner & Clifton, 2009; Sereno & Rayner, 2003), time course estimates differ between event-related brain potentials (ERPs) and eye movements during reading, the two techniques that have long been the methods of choice for examining timing information in the psycholinguistic literature on sentence processing. For a recent discussion in the context of the neurobiology of sentence processing, see Bornkessel-Schlesewsky et al. (2016).

Differing perspectives

The time course of sentence processing in the brain is subject to substantial debate, without a consensus view yet having emerged. In the following, we will thus discuss a variety of perspectives. These will be based primarily on ERP data, which is still the most widely used neurocognitive method for studying the time course of sentence processing.

Component Mapping and Absolute Timing

Originally, ERP-based research into the time course of sentence processing closely mirrored the cognitive perspective that had been developed on the basis of behavioral results. Thus, ERP components such as the N400 and P600 were viewed as correlates of linguistic domains (semantic and syntactic processing, respectively) and the relative timing of these components, as well as their interaction or mutual independence, was thus thought to shed light on the organization of the language architecture (e.g. Friederici, Pfeifer, & Hahne, 1993; Hagoort, Brown, & Osterhout, 1999; Osterhout & Nicol, 1999; among many others).

This perspective forms part of timing assumptions set out as part of Friederici's neurocognitive model of auditory sentence processing (Friederici, 1995, 1999, 2002, 2009, 2011) and Hagoort's MUC model (Hagoort, 2003, 2005, 2013) (see earlier discussion for the anatomical assumptions of these models). In the spirit of the classic modularity versus interactivity debate, the neurocognitive model posits that different information sources are processed in several successive processing stages, which are organized serially, while the MUC model advocates an interactive processing architecture. In each case, evidence for the respective view was provided by an assessment of ERP component timing. Both models subscribe to the view that the N400 and left-anterior negativity (LAN) effects are related to semantic and (morpho-)syntactic aspects of processing, respectively. The MUC model also posits a syntactic role for the P600, while the neurocognitive model assumes that the P600 reflects the late integration of syntactic and semantic information that was processed separately in preceding phases. By contrast, the MUC model assumes that there is no priority for any one information source over another during sentence interpretation ("one-step" interpretation) and that the relative timing of when a particular information source is used depends on its availability in the input signal (Hagoort, 2008). The one-step-interpretation assumption of the MUC model is supported by results showing that sentence-internal and sentence-external information all modulate the N400 component, with no evidence for a different time course depending on the source of the information (see Hagoort & van Berkum, 2007, for a detailed review of the relevant studies).

As in the cognitive domain, the debate between modular and interactive neurocognitive models of sentence processing remains unresolved, even after several decades of work on this subject. Furthermore, continuing progress in the field has revealed challenges to some of the basic assumptions underlying the component mapping approach:

(a) *Absolute timing*. Several observations have called into question the assumption that ERP component latencies provide absolute estimates of timing information. The first stems from measures of eye movements during reading, which, as briefly noted earlier, sometimes provide different timing estimates to ERPs. This is perhaps most readily apparent with regard to the N400 component, which typically shows an onset latency of a little more than 200 milliseconds (ms) in young adults (Kutas & Iragui, 1998, report an average onset latency of 236 ms for adults in their twenties) and is highly stable in terms of its timing (e.g., Federmeier & Laszlo, 2009). The N400 is reliably modulated by word frequency (at least for words occurring early on in a sentence; Van Petten & Kutas, 1990), a factor that is also known to affect the duration of the first fixation on a word during reading (e.g., Inhoff & Rayner, 1986). Since fixations last approximately 200–250 ms on average for English (Rayner, 1998) and saccade programming is thought to require approximately 150–175 ms (Rayner, Slowiaczek, Clifton, & Bertera, 1983), word frequency appears to influence eye movements at a point in time that *precedes* the onset of the N400 (for discussion, see Bornkessel & Schlesewsky, 2006; Rayner & Clifton, 2009; Sereno & Rayner, 2003). This suggests that latencies of components such as the N400 and P600 may not be reliable indicators of when a particular information source first becomes available or when it is first utilized during sentence processing.

A second and related observation stems from the ERP domain itself. If components such as the N400 do not provide absolute timing information, perhaps markers of this information should be sought earlier on in the ERP record. Indeed, there have been a number of reports of language-related ERP effects "before the N400" (e.g., Dien, 2009). These include word frequency-based modulations of the N100 (Sereno, Rayner, & Posner, 1998) and modulations of the mismatch negativity (MMN), which peaks between approximately 100 and 250 ms post-stimulus-onset, by morphosyntactic violations presented as part of an oddball design (e.g., Hasting, Kotz, & Friederici, 2007). Recent MEG studies have also provided converging evidence for early effects, for example by demonstrating a dissociation of brain responses to words and pseudowords from as early as 50 ms onward

(MacGregor, Pulvermüller, van Casteren, & Shtyrov, 2012) or a modulation of the visual M100 by syntactic (Dikker, Rabagliati, & Pylkkänen, 2009) and lexical-semantic violations (Dikker & Pylkkänen, 2011) in highly predictive contexts. Possibly, findings such as these should be taken to indicate that ERPs and event-related magnetic fields (ERFs) *do* provide absolute timing information once early components—rather than "late" components such as the N400—are taken into account. We shall return to this perspective later.

(b) *1:1 component mapping*. Though highly appealing, the notion that language-related ERP components can be used as diagnostic indicators of particular linguistic or cognitive domains (e.g., the N400 as a correlate of lexical-semantic processing or declarative memory contributions to language [Ullman, 2001] versus the LAN/P600 as correlates of morphosyntactic processing or procedural memory) is now challenged by a continually increasing number of findings. On the one hand, the occurrence of monophasic P600 effects for certain types of semantic violations—particularly violations in which a plausible sentence would obtain if thematic role assignments to arguments were reversed (e.g., "The hearty meals were *devouring* . . ."; Kim & Osterhout, 2005)—has been discussed intensely in the literature on the electrophysiology of language over the past decade (e.g., Hoeks, Stowe, & Doedens, 2004; Kim & Osterhout, 2005; Kolk, Chwilla, van Herten, & Oor, 2003; Kuperberg, Sitnikova, Caplan, & Holcomb, 2003; among many others; for reviews, see Bornkessel-Schlesewsky & Schlesewsky, 2008; Brouwer, Fitz, & Hoeks, 2012; van de Meerendonk, Kolk, Chwilla, & Vissers, 2009). In addition, many studies employing "traditional" semantic violations in the style of Kutas and Hillyard's famous "He spread the warm bread with *socks*" (Kutas & Hillyard, 1980) have observed N400s followed by P600 effects, and P600 effects have also been observed in response to other types of incongruencies such as orthographic violations (Vissers, Chwilla, & Kolk, 2006), thus leading several groups to suggest more general interpretations of the P600 (e.g., as a correlate of "conflict monitoring": Kolk et al., 2003; van de Meerendonk et al., 2009) or an instance of the domain-general P300 (e.g., Coulson, King, & Kutas, 1998; Gunter, Stowe, & Mulder, 1997; Sassenhagen, Schlesewsky, & Bornkessel-Schlesewsky, 2014).

While less well-known than semantic P600s, syntax- or morphosyntax-related N400 effects have also been reported in a range of studies, for example for case violations (Choudhary, Schlesewsky, Roehm, & Bornkessel-Schlesewsky, 2009; Frisch & Schlesewsky, 2001, 2005; Mueller, Hahne, Fujii, & Friederici, 2005; Mueller, Hirotani, & Friederici, 2007), gender incongruencies (Wicha, Moreno, & Kutas, 2004), and word order variations (Bornkessel, McElree, Schlesewsky, & Friederici, 2004; Haupt, Schlesewsky, Roehm, Friederici, & Bornkessel-Schlesewsky, 2008). In summary, all of these results suggest that ERP components do not reflect a clear-cut functional divide between linguistic subdomains and that somewhat more general explanations may rather be required.

Problems with Absolute Timing: MMN Evidence for Early, Cascaded Information Processing

As already discussed in some detail, there is considerable evidence to suggest that the latency of classic language-related ERP components such as the N400, LAN, and P600 does not provide an adequate estimate of absolute time-course information. Within the neurocognitive domain, this perspective has been advocated for some time by Pulvermüller and colleagues, drawing primarily on experimental paradigms using the mismatch negativity (MMN). The MMN typically occurs in response to deviant stimuli in oddball paradigms (i.e., stimuli that occur infrequently within sequences of high probability "standards"; for reviews, see Garrido, Kilner, Stephan, & Friston, 2009; Kujala, Tervaniemi, & Schröger, 2007). Traditionally, MMN effects are elicited using relatively simple stimuli (e.g., tone sequences), but Pulvermüller and colleagues have extended this line of research to considerably more complex stimuli, including minimal phrases such as "we come" or, as a violation condition, "we comes" (Pulvermüller & Shtyrov, 2003; Shtyrov & Pulvermüller, 2002). In comparison to the same word presented out of context (i.e., "comes" preceded by a non-linguistic noise mimicking the spectral envelope of the word "we"), the ungrammatical string elicited a larger MMN than the grammatical string between 100 and 150 ms after the acoustic divergence point between the two strings (for morphosyntactic MMN effects in German, see Hasting et al., 2007). Semantic effects have also been observed (Menning et al., 2005; Shtyrov & Pulvermüller, 2007).

Studies such as these have been taken to suggest that linguistic information sources such as syntax and semantics are processed in "near simultaneity" and in considerable earlier time windows than traditional language-related ERP components such as the N400 suggest (Pulvermüller, Shtyrov, & Hauk, 2009). The supporting evidence from MMN paradigms is sometimes viewed as problematic due to the highly repetitive nature of the stimulation and the lack of lexical variation (i.e., an experiment may consist simply of a large number of repetitions of "he walks" and "he walk," with one the standard and one the deviant). However, since syntactic or semantic violation deviants are always contrasted against grammatical deviants in these paradigms, the linguistic properties of the stimulus obviously play at least some role in engendering the larger MMN response to incongruous stimuli. This could be explained by assuming that the first word in a minimal phrase such as "he walks" sets up certain expectations with regard to possible continuations that are commensurate with the prior experience of the language-processing system. Clearly, this does not preclude additional expectations or predictions being established by the intra-experimental probability of the different stimuli (i.e. that a standard is more likely to occur than a deviant), but it appears entirely plausible as an additional source of prediction (for an account of the MMN within a predictive-coding-based framework, see Friston, 2005; Garrido et al., 2009).

In summary, a perspective advanced most prominently by Pulvermüller and colleagues (among other researchers) assumes that ERP/MEG components are informative with regard to absolute time course information, but proposes that the relevant effects occur in a time range prior to 200 ms and, therefore, precede typical language-related components such as the N400. Since these early effects are thought to arise from the near-simultaneous activation of word-specific cortical circuits, the differing conduction delays within which account for the apparent cascade of effects, this account essentially abolishes the idea of component mapping. As we have suggested here, however, predictive processing may also play an important role in engendering—or at least modulating—the effects under discussion, and this aspect may help to link the relevant explanations to sentence-level processing.

Predictions, Predictions, Predictions

The importance of top-down predictions is emphasized more strongly in an approach that has been championed by Dikker, Pylkkänen, and colleagues. Using MEG, these researchers have repeatedly shown that sentence-level (syntactic and semantic) incongruities engender modulations of the visual M100, a component that is typically localized to visual cortex (Dikker & Pylkkänen, 2011; Dikker et al., 2009; Dikker, Rabagliati, Farmer, & Pylkkänen, 2010). In the syntactic domain, these early effects have been observed for word category violations (e.g., "the boys heard Joe's **about** . . ." or "the tastelessly **soda** . . ."). In the semantic domain, they have been demonstrated using a picture-word matching paradigm (e.g., the noun phrase "the apple" following an image of an apple (+predictive, +match), a picture of a banana (+predictive, –match), a picture of a shopping bag with many items (–predictive, +match) or a picture of Noah's ark with many animals (–predictive, –match).

The early latency of the M100, as well as its likely source localization, suggests that the effects in question may be indexing prediction mismatches at a rather early, sensory level. In other words, if the predictive context is strong enough, predictions extend not only to abstract features of an upcoming linguistic item (e.g.. word class, semantic category, etc.), but also to its sensory properties (i.e., a concrete word form). Similar effects have been observed in the auditory domain, as demonstrated by the so-called phonological mapping negativity (PMN). The PMN, previously labeled phonological mismatch negativity and analyzed by some as an instance of the N200 component (van den Brink, Brown, & Hagoort, 2001, 2006), is a negativity with a peak latency of approximately 250–300 ms, which occurs in response to phonologically unexpected input (Connolly & Phillips, 1994). As recently demonstrated by Newman and Connolly (2009), the PMN is independent of whether the current input item is a word or a nonword, thus suggesting that it reflects a purely form-based expectation mismatch. At least to some degree, an account of language-related ERP components that focuses on sensory predictability shifts the burden of explanation for observed ERP or ERF effects from the current input item to the preceding linguistic context. In other words, when evaluating time-course information, the properties of the current stimulus item may be less important than the predictive capacity of the context in which it is encountered.

This perspective is highly compatible with a hierarchically organized predictive coding architecture (Friston, 2005, 2010), in which predictions are passed from higher to lower areas within the cortical hierarchy and, depending on their specificity, can lead to prediction errors at any hierarchical level. Thus, the prediction error signal itself is not necessarily diagnostic of any particular functional interpretation, but rather varies as a function of where within the overall architecture the prediction error is registered.

Multimodal Processing and the Integration of Multiple Information Sources

The notion of prediction also plays a crucial role in an account of language-related ERP components, and specifically the N400, which abstracts away from time-course information to a relatively large degree (Kutas & Federmeier, 2011). This perspective builds on the observation that (a) the N400 is not parsimoniously described in relation to lexical (and pre-lexical, post-lexical, etc.) processing, since, for example, it also responds to nonword stimuli as long as they are meaningful in a given context (Federmeier & Laszlo, 2009, for an overview); and (b) the N400 is remarkably stable with respect to its latency (see earlier discussion). Accordingly, Federmeier, Kutas, and colleagues argue that the N400 should be viewed as indexing a period of convergence between multiple, multimodal information sources, during which meaning is constructed in a dynamic and context-dependent manner. In other words, the N400 indexes the “transition from unimodal to multimodal processing (e.g., from word form to the concept that word brings to mind)” and “reflect[s] the activity in a multimodal long-term memory system that is induced by a given input stimulus during a delimited time window as meaning is dynamically constructed” (Kutas & Federmeier, 2011, p. 640).

This perspective, too, emphasizes the crucial role of prediction during language processing, since linguistic context is assumed to pre-activate particular linguistic features as well as their combination. This pre-activation process modulates the dynamic construction of meaning, as described earlier, and hence impacts on N400 amplitude. Like the perspectives discussed in the preceding sections, it thus de-emphasizes the notion of component mapping and, though it does not focus on early language-related ERP components, it shares with Pylkkänen and colleagues the assumption that predictive processing plays a crucial role in language comprehension. In view of the focus on the N400 and the fixed latency of this component, however, detailed time-course considerations do not feature as part of this account.

The Interplay Between Top-Down and Bottom-Up Information Sources

In addition to the focus on prediction that has been central to the discussion in the preceding subsections, a range of findings now demonstrate that top-down predictability or "pre-activation" is not the sole determinant of neurophysiological effects during sentence comprehension. Rather, the "balance" between top-down and bottom-up influences needs to be taken into account. Once again, a great deal of the relevant evidence stems from the N400 ERP component. A recent finding which shows that N400 amplitude is modulated by properties of the current stimulus, rather than the preceding context, was reported by Laszlo and Federmeier (2011). They showed that N400 amplitudes are higher for input items—both words and letter strings—with more or higher frequency orthographic neighbors and lexical associates. This result also provides compelling evidence against a view of the N400 as a correlate of lexical access or post-lexical processing, since accounts along these lines should predict differences between word and nonword stimuli. The need to consider the integration of top-down and bottom-up information was further emphasized by Lotze, Tune, Schlesewsky, and Bornkessel-Schlesewsky (2011), who found that an unpredictable physical change from normal orthography to a capitalized sentence-final word almost completely neutralized an implausibility-based N400 effect on that word, while a change from all capitalized input to a lower-case sentence-final word had no effect on the N400. Clearly, the attenuation of the N400 must be attributable to bottom-up stimulus features in this study, since top-down factors did not change between conditions. A somewhat similar result was reported by Delaney-Busch and Kuperberg (2013), who found that N400 effects for incongruous scenarios were neutralized when the critical word was an emotion word (of positive or negative valence). A possible explanation for these results is that, in line with Bar's (2003) assumptions concerning visual object recognition (see also earlier discussion in this chapter), very basic and salient stimulus features (e.g., sudden capitalization as a visual "pop out" or high emotional valence) are rapidly projected to prefrontal cortex (or other higher-level regions within the cortical hierarchy) via long-range feedforward connections, thus enabling these features to lead to a top-down modulation of plausibility or congruity effects.

If this proposal indeed turns out to be viable, it could provide the basis for a new approach for inferring the organization of the neural language architecture. Rather than basing arguments on temporal precedence, investigations should focus more closely on functional precedence: if an information source A can "block" the effects typically associated with a second information source B, this suggests that A takes functional (hierarchical) precedence over B. Depending on the particular type of manipulation examined, further inferences can be drawn regarding the likely nature of the blocking effect (i.e., whether it results from a feedforward influence, as is likely the case for concurrent word category and semantic violations, or from a combination of long-range feedforward and feedback connections, as may be the case for the orthographic and emotional influences on congruity effects).

The Emerging Picture

As noted earlier, our understanding of the time course of sentence processing in the brain is still woefully incomplete and, in particular, we have a long way to go in advancing toward a truly neurobiologically grounded perspective in this respect. Nevertheless, the preceding discussion shows that substantial progress has been made. Here, we attempt to summarize some of the insights emerging from this overall picture:

(a) ERP components appear to be less specific for particular cognitive—and specifically, particular linguistic—representations and/or operations than was once thought. Accordingly, more and more accounts are adopting more general mechanistic interpretations of the components and no longer are emphasizing the distinction between them, as was previously the norm.
(b) The importance of top-down versus bottom-up information has emerged as a major topic in the literature on sentence processing (e.g., Federmeier, 2007; Federmeier & Laszlo, 2009; Kutas & Federmeier, 2011; Lotze et al., 2011; Newman & Connolly, 2009; Tune et al., 2014). This view includes a critical role for prediction (DeLong, Urbach, & Kutas, 2005; Dikker & Pylkkänen, 2011; Dikker et al., 2010; Federmeier, Kutas, & Schul, 2010) and is also highly compatible with the assumption of a hierarchically organized cortical architecture with predictive coding and asymmetric forward and backward connections (Friston, 2005, 2010)

What are the consequences of these insights for our understanding of the time course of sentence processing in the brain? While the question remains difficult, we can draw at least the following minimal conclusion. If we want to think in cognitive terms, there is a high likelihood of a cascaded architecture (though an "imperfect" one, due to the feedback connections and long-range feedforward connections described throughout this chapter). This also means that specific information sources are less important than was long thought for the processing of the current input item in comparison to their predictive capacity for upcoming input. This view allows for a new synthesis of the classic modular and interactive views: it suggests that modular models placed too much emphasis on bottom-up information and a feedforward information flow, while interactive models placed too much emphasis on top-down information and a parallel information flow between all available information sources or representations.

Summary and Outlook

In this chapter, we have attempted to summarize the current state of the art with regard to sentence processing in the brain. As will be readily apparent to the reader, there is much left to do in this domain. Nevertheless, it is hopefully also clear that the field of sentence processing has come a long way since its inception. While early approaches focused mainly on testing the assumptions of linguistic theories (e.g., Clifton, Kurcz, & Jenkins, 1965; Mehler, 1963; Miller, 1962), later perspectives were concerned with uncovering more general cognitive-processing mechanisms (e.g., Frazier, 1987; Gibson, 1998; Lewis, 1996; Lewis, Vasishth, & Van Dyke, 2006; MacDonald et al., 1994; McElree, 1993, 2006; Rayner et al., 1983; Trueswell & Tanenhaus, 1994). For neurolinguistics, the challenge now lies in developing true neurobiological models of sentence processing that will explain how it emerges from basic principles of neural information processing in both time and space.

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CHAPTER 28

COMPREHENSION OF METAPHORS AND IDIOMS

An Updated Meta-analysis of Functional Magnetic Resonance Imaging Studies

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Everyday language in both speech and written language is abundant in expressions that, when taken literally, are wrong (at least in the aforementioned context). These expressions are referred to as *nonliteral language*. Two important forms of nonliteral constructions are metaphors (such as "neuroimaging is a gold mine") and idioms (such as "it's raining cats and dogs"). Other types include ironic expressions, proverbs, and metonymy. For linguists, nonliteral language (or "figurative" language, a term used more often in the context of research, although presumably less exact) is interesting because of its sheer frequency of occurrence alone. While corpus linguists still debate whether metaphors (Cameron & Deignan, 2006; Stefanowitsch & Gries, 2007) or idioms (Simpson & Mendis, 2003; Van Lancker-Sidtis & Rallon, 2004) are more frequent in everyday speech, there is consensus that both forms are essential parts of everyday speech (Lakoff & Johnson, 2008). At first glance that seems inappropriate. Nonliteral language violates the maxim to speak in the utmost understandable form while avoiding ambiguity. Nevertheless, it is often used and therefore obviously serves important communicative functions (Gibbs Jr. & Colston, 2012; Lakoff & Johnson, 2008), presumably including being polite, of higher emotional precision, better remembered or—often enough—the only way the speaker has to express an issue (Colston & Katz, 2004).

This chapter covers the underlying neurobiology of metaphor and idiom comprehension. The topic has gained interest in many different research fields. For decades, it has been claimed that clinical populations may have a selective deficit in metaphor comprehension, including patients with damage to the right hemisphere of the brain (Brownell, Simpson, Bihrle, Potter, & Gardner, 1990; Winner & Gardner, 1977) and those with disorders such as schizophrenia (Chapman, 1960; Rapp, 2009; Rapp, Langohr, Mutschler, & Wild, 2014) and autism (Gold, Faust, & Goldstein, 2010). The majority of research has been focused on these disorders, but some studies have investigated other conditions, including dementias (Rapp & Wild, 2011), William's syndrome (Annaz et al., 2009), depression (Rapp & Schmierer, 2010), traumatic brain injury (Martin & McDonald, 2005), relational aggression (Blasko & Kazmerski, 2006), schizotypal personality traits (Ettinger et al., 2015), Parkinson's disease (Gutmann, 2009), amyotrophic lateral sclerosis (ALS; Bambini et al., 2016), and other developmental disorders (Rapp & Wild, 2011). Paradigms on metaphor and idiom comprehension are also used as clinical and research tools to investigate embodiment (Denke, Rotte, Heinze, & Schaefer, 2014; Gibbs, Lima, & Francozo, 2004) and motor language (Raposo, Moss, Stamatakis, & Tyler, 2009), social cognition (Landau, Meier, & Keefer, 2010; Langdon, Coltheart, Ward, & Catts, 2002), aphasia (Papagno & Caporali, 2006), intelligence (Jäger & Althoff, 1994), and coverbal gestures (Straube, Green, Sass, & Kircher, 2014). It is therefore not surprising that the number of studies on the neural correlates of these forms of communication has consistently increased, especially within the last 10 years. This chapter reviews the functional magnetic resonance imaging studies (fMRI) on metaphor and idioms.

A META-ANALYSIS ON METAPHOR COMPREHENSION

Findings of fMRI studies (see Heim & Specht, Chapter 4 in this volume) can be summarized using coordinate-based meta-analyses (activation likelihood estimation [ALE]; see BrainMapDevelopmentTeam, 2013; Eickhoff et al., 2009). In this type of analysis, the coordinates reported in the studies are used and, if necessary, transformed into one coordinate system: either Talairach space (Talairach & Tournoux, 1988) or Montreal Neurological Institute (MNI) space (Tzourio-Mazoyer et al., 2002). Briefly, this analysis involves fitting the coordinate data to a Gaussian curve in order to identify any activation clusters in the brain. The research tool identifies consistent regions of activation across a collection of fMRI studies and shows where the reported activations converge (Eickhoff et al., 2009). Meta-analyses of fMRI data have advantages and disadvantages. A disadvantage of such meta-analyses is that their interpretations can be limited when only a small number of foci have been reported in the available literature, and that it might overestimate the effect of studies with low or "liberate" chosen activation thresholds.

So far, five meta-analyses for metaphors (Bohrn, Altmann, & Jacobs, 2012; Rapp, Mutschler, & Erb, 2012; Vartanian, 2012; Yang, 2014; Yang & Shu, 2016) and one for idioms (Rapp et al., 2012) have been published. The meta-analyses show comparable results, which is not astonishing, given that they rely on overlapping studies; however, they slightly differ in their interpretation. Here, we present an updated version of our previous meta-analysis (Rapp et al., 2012), which includes more recent data.

fMRI Literature on Metaphor

First, our previous systematic literature search (Rapp et al., 2012) was retrofitted with the new publications since 2012. Studies were identified by PUBMED and "Web of Science" (2016) databases, including targeted search for important researchers in the field and search within citations of previous studies. Our meta-analysis of 2012 (Rapp et al., 2012) for metaphors included 16 studies.

Because of our methodological criteria, this meta-analysis includes not all available work. We did not include studies using positron emission tomography (PET), near-infrared spectroscopy (NIRS; see Minagawa & Cristia, Chapter 7 in this volume) or electroencephalograph (EEG) technology (see Leckey & Federmeier, Chapter 3 in this volume), although some of these studies report activation maxima (Bottini et al., 1994; Proverbio, Crotti, Zani, & Adorni, 2009; Schneider et al., 2014; Sotillo et al., 2005). Our rationale for this was that these research methods may have higher variation in the localization of maxima (BrainMapDevelopmentTeam, 2013). Further, we included only reported whole brain analyses, while region of interest (ROI) data were not recommended. This followed the rationale that ROI analyses might bias results toward the same ROIs. Studies that did not report the contrast for metaphors > literal stimuli were not included. Further, in the analysis presented here, activations for metaphors > meaningless word combinations or metaphors > meaningless sentences were not considered. The differences in the inclusion criteria and in the number of included studies could explain the slight differences in the results between the other published meta-analyses and this study.

The systematic literature search since 2012 yielded significant additional results. Table 28.1 shows the available studies until December 2015. Twenty-seven studies were included in the meta-analysis for metaphors (see Rapp, 2012, for a narrative review of the older studies and brain lesion research). In recent years, there has been a significant increase in the quantity of literature, and the methodological quality of these studies has further improved. For example, the average number of metaphoric stimuli has (again) increased across all studies to 50.7 (see Table 28.1).

All metaphor and idiom studies together contained 875 study subjects, while the meta-analysis on metaphors consists of data from only 460 subjects. These studies investigated diverse aspects and several languages. There are now investigations in eight languages. Shibata et al. (Shibata, 2011; Shibata et al., 2012) reported new fMRI data in the Japanese language, while Obert et al. (2014) first reported fMRI data in the French and Dutch (Samur, Lai, Hagoort, & Willems, 2015) languages. New comparisons for different types of non-literal language were provided by Prat and Just (Prat, Mason, & Just, 2012) with ironic stimuli, while two other studies, one in English (Desai, Conant, Binder, Park, & Seidenberg, 2013) and one in Italian (Romero Lauro, Mattavelli, Papagno, & Tettamanti, 2013), have idioms as stimuli in addition to metaphors. New data with German metaphors was presented by Forgacs et al. (2012); Bohrn, Altmann,

Table 28.1 Overview of functional magnetic resonance imaging (fMRI) studies on metaphor and idiom comprehension: Studies Included in the Updated fMRI Meta-analysis.

		Year	Non-literal Language Type	Language	Number of Subjects	Stimulus Level	Novel Stimuli	Salient Stimuli	Number of Non-literal Stimuli
1	Rapp et al., 2004	2004	Metaphor	German	15	Sentence	x		30
2	Mashal et al., 2005	2005	Metaphor	Hebrew	15	Word	x	x	2 x 24
3	Eviatar and Just, 2006	2006	Metaphor	English	16	Text vignette		x	2 x 9
4	Lee and Dapretto, 2006	2006	Metaphor	English	12	Word		x	16
5	Stringaris et al., 2006	2006	Metaphor	English	12	Sentence		x	?
6	Aziz-Zadeh et al., 2006	2006	Metaphor	English	12	Sentence		x	15
7	Wakusawa et al., 2007	2007	Metaphor	Japanese	38	Sentence		x	14
8	Ahrens et al., 2007	2007	Metaphor	Chinese	8	Sentence	x	x	2 x 14
9	Stringaris et al., 2007	2007	Metaphor	English	11	Sentence		x	25
10	Mashal et al., 2007	2007	Metaphor	Hebrew	15	Word	x	x	2 x 24
11	Rapp et al., 2007	2007	Metaphor	German	17	Sentence	x		60
12	Zempleni et al., 2007	2007	Idiom	Dutch	15	Sentence		x	64 + 32
13	Shibata et al., 2007	2007	Metaphor	Japanese	13	Sentence	x		21
14	Mashal et al., 2008	2008	Idiom	Hebrew	14	Sentence		x	50
15	Lauro et al., 2008	2008	Idiom	Italian	22	Sentence		x	62
16	Boulenger et al., 2009	2009	Idiom	English	18	Sentence		x	26
17	Chen et al., 2008	2008	Metaphor	English	14	Sentence		x	35

(*continued*)

Table 28.1 Continued

		Year	Non-literal Language Type	Language	Number of Subjects	Stimulus Level	Novel Stimuli	Salient Stimuli	Number of Non-literal Stimuli
18	Mashal et al., 2009	2009	Metaphor	Hebrew	15	Sentence	x		25
19	Hillert and Buracas, 2009	2009	Idiom	English	10	Sentence		x	100
20	Raposo et al., 2009	2009	Idiom	English	22	Sentence		x	56
21	Yang et al., 2009	2009	Metaphor	English	18	Sentence	x	x	100
22	Schmidt and Seger, 2009	2009	Metaphor	English	10	Sentence	x	x	3 x 24
23	Yang et al., 2010	2010	Metaphor	English	18	Sentence	x		2 x 23
24	Mashal and Faust, 2010	2010	Metaphor	Hebrew	10	Text		x	28 1
25	Mejía-Constaín et al., 2010	2010	Metaphor	French	2 x 10	Word		x	25
26	Desai et al., 2011	2011	Metaphor	English	22	Sentence	x	x	81
27	Diaz et al., 2011	2011	Metaphor	English	16	Sentence	x	x	2 x40
28	Bambini et al., 2011	2011	Metaphor	Italian	10	Two-sentence passage	x	x	40
29	Diaz and Hogstrom, 2011	2011	Metaphor	English	16	Two-sentence passage	x	x	2 x 40
30	Uchiyama et al., 2012	2012	Metaphor	Japanese	20	Text vignette		X	2 x 20
31	Shibata, 2011	2011	Metaphor	Japanese	12	Sentence	x		10
32	Prat et al., 2012	2012	Metaphor Irony	English	24	Text vignette		x	2 x 10
33	Cardillo et al., 2012	2012	Metaphor	English	20	Sentence	x	x	2 x 60
34	Subramaniam et al., 2012	2012	Metaphor	English	11	Word	x	x	2 x 68
35	Forgacs et al., 2012	2012	Metaphor	German	40	Word	x	x	2 x 40

36	Shibata et al., 2012	2012	Metaphor	Japanese	24	Sentence	x		2 x 20
37	Lacey et al., 2012	2012	Metaphor	English	7	Sentence		x	54
38	Kana et al., 2012	2012	Idiom	English	36	Sentence		x	9
39	Subramaniam et al., 2013	2013	Metaphor	English	14	Word	x	x	2 x 68
40	Desai et al., 2013	2013	Idiom Metaphor	English	27	Sentence		x	2 x 40
41	Bohrn et al., 2012b	2012	Proverb	German	26	Sentence	x	x	4 x 40
42	Mashal et al., 2013	2013	Metaphor	Hebrew	14	Word	x	x	2 x 24
43	Romero Lauro et al., 2013	2013	Idiom Metaphor	Italian	24	Sentence		x	2 x 21
44	Schuil et al., 2013	2013	Idiom	Dutch	20	Sentence		x	100
45	Klepousniotou et al., 2014	2014	Metaphor	English	15	Word		x	30
46	Benedek et al., 2014	2014	Metaphor	German	28	Production			24
47	Mashal et al., 2014	2014	Metaphor	Hebrew	12	Word	x	x	2 x 24
48	Obert et al., 2014	2014	Metaphor	French	19	Sentence context	x		24
49	Citron and Goldberg, 2014	2014	Metaphor	German	26	Sentence		x	37
50	Samur et al., 2015	2015	Metaphor	Dutch	20	Text vignette		x	60
51	Lai et al., 2015	2015	Metaphor	English	22	Sentence	x	x	27
52	Yang et al., 2016	2016	Idiom	Chinese	20	Sentence		X	96

Lubrich, Menninghaus, and Jacobs (2012); and by Citron and Goldberg (2014). Of special interest is the study by Benedek et al. (2014), which first investigated the production of metaphors in the German language using fMRI. Another study in Hebrew was presented by Mashal et al. (Mashal, Vishne, Laor, & Titone, 2013), while eight additional studies in English (Cardillo, Watson, Schmidt, Kranjec, & Chatterjee, 2012; Desai et al., 2013; Klepousniotou, Gracco, & Pike, 2014; Lacey, Stilla, & Sathian, 2012; Lai, van Dam, Conant, Binder, & Desai, 2015; Prat et al., 2012; Subramaniam, Beeman, Faust, & Mashal, 2013; Subramaniam, Faust, Beeman, & Mashal, 2012) showed that it is the most frequent language. This makes clear as well that the non-English studies, with 49% of the total studies and 45% of the trial participants, play a significant role. To date, metaphors in a participant's second language (L2) have not yet been studied using fMRI, although there are numerous "offline" (without fMRI) studies on this subject that have presented experimental data (Charteris-Black, 2002; Heredia & Cieslicka, 2015; Littlemore, 2001; Mashal, Borodkin, Maliniak, & Faust, 2015; Tuerker, 2016).

Table 28.1 shows whether salient or non-salient stimuli were used because this distinction plays an important role in the literature (Bowdle & Gentner, 2005; Desai, Binder, Conant, Mano, & Seidenberg, 2011; Giora, 1997; Rapp et al., 2012). Classification of salient stimuli followed the classification scheme given by the authors' published classification. If the authors provided no description, classification was based on the stimulus examples provided using the Google corpus (Rapp et al., 2012). Although familiarity with metaphors is not identical to their salience (Giora, 1999; Rapp & Wild, 2011), familiar stimuli in this case were counted as salient. The procedure for data analysis in this follow-up meta-analysis was identical to Rapp et al. (2012). ALE analysis was implemented using the software update GingerALE 2.3 for Windows (Eickhoff et al., 2009; www.brainmap.org). After identification of the relevant studies, the reported activation maxima were extracted from the publications. Coordinates reported in Talairach space were transformed into MNI coordinates using the "Talairach to MNI (SPM)" tool implemented in GingerALE (Fox et al., 2013) 2.3 (tal2icbm_spm.m).

RESULTS

The 27 studies using metaphors reported 271 foci in 460 study participants. Figure 28.1 shows a projection of these coordinates onto a brain surface. Each dot indicates a stronger reported activation for metaphors > literal control stimuli. An important limitation of this type of analysis is that it—like perhaps fMRI activation itself—gives limited information about its functional importance. Nevertheless, several things become clear when we look at the distribution; the pattern of activation points strongly against a "metaphor center" in the brain. Instead, a distributed network is responsible for the understanding of metaphors. Figure 28.1 shows significant similarity to that found in

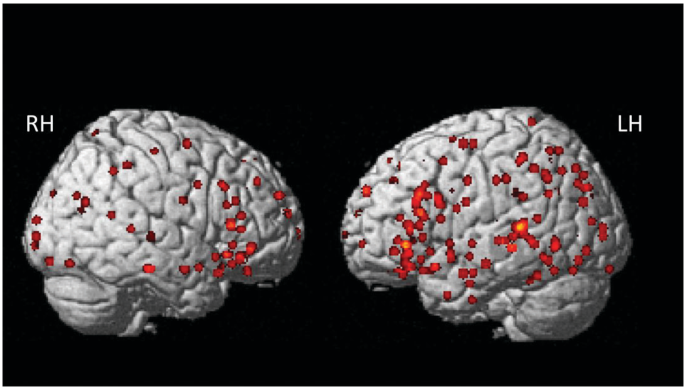

FIGURE 28.1. Projection onto a brain surface: 271 foci reported in 27 studies for differential contrasts metaphor > literal stimuli; 86 (31%) are located in the right hemisphere.

comparable studies on the semantic comprehension of literal language (Binder, Desai, Graves, & Conant, 2009). In addition, its lateralization is similar to the pattern found generally in semantic comprehension (Binder et al., 2009; Rapp et al., 2012). Laterality has traditionally been a focus of non-literal language research (Burgess & Chiarello, 1996; Lindell, 2006; Zaidel, Kasher, Soroker, & Batori, 2002). Out of the 271 foci, 86 (31%) are located in the right hemisphere. Compared to our previous meta-analysis (2012), the relative proportion of right hemispheric foci has decreased slightly (from 35%), which contradicts early fMRI studies that may have underestimated the proportion in the right hemisphere. Table 28.2 shows the results of the meta-analysis.

Table 28.2 Activation likelihood estimation (ALE) meta-analysis of functional magnetic resonance imaging (fMRI) studies with metaphoric stimuli (metaphor > literal, whole brain analysis).

Cluster #	Hemisphere	Region	Brodmann Area	*x*	*y*	*z*	Volume (mm^3)
1	LH	Inferior frontal gyrus	45	−46	22	14	2,336
	LH	Middle frontal gyrus	9	−52	22	28	
2	LH	Superior temporal gyrus	22	−56	−40	8	1,368
3	LH	Parahippocampal gyrus	36	−34	−34	−16	960
	LH	Parahippocampal gyrus	36	−30	−38	−10	
4	LH	Inferior frontal gyrus	47	−46	30	−8	712
5	LH	Superior frontal gyrus	6	−4	16	50	656

Meta-analysis metaphor

Brain Regions Involved in Metaphor Comprehension

The strongest cluster can be found in the left inferior frontal gyrus (IFG) in Brodmann area 45, with expansion into BA 9 and the middle frontal gyrus. Numerous studies contribute to this cluster (Ahrens et al., 2007; Forgacs et al., 2012; Lee & Dapretto, 2006; Mashal, Faust, Hendler, & Jung-Beeman, 2007, 2009; Mashal et al., 2013; Shibata et al., 2012). In our previous study (Rapp, Leube, Erb, Grodd, & Kircher, 2004), we argued that the anterior-inferior part of the IFG could bring together the two semantic entities within a metaphor, which are the tenor and the vehicle. This brain region could be responsible for the "mapping" process during metaphor comprehension. However, this view is controversial. Other authors attributed this process to the right hemisphere (Bottini et al., 1994; Burgess & Chiarello, 1996; Toga & Thompson, 2003; Yang, 2014). It was recently noted that the process of bringing together semantic entities might better be called "binding" during metaphor comprehension, instead of "mapping" (Strack, 2016). In our original papers (Kircher, Leube, Erb, Grodd, & Rapp, 2007; Rapp, Erb, Grodd, Bartels, & Markert, 2011; Rapp et al., 2004; Rapp, Leube, Erb, Grodd, & Kircher, 2007), we suggested specificity for the anterior-inferior part of the left IFG. However, the interim literature reveals a more distributed involvement within the left IFG (Figure 28.1). In addition to the ALE analysis in Table 28.2, we anatomically classified (Rapp, unpublished data) the data of today's literature. This includes a spatial uncertainty because some of the foci were converted from Tailairach into MNI coordinate systems (e.g., Lancaster et al., 2007). The localization of each of the foci reported in the literature was then assigned to an anatomical region. Automated anatomical labeling (AAL; Tzourio-Mazoyer et al., 2002) and xjview (Cui, Li, & Song, 2011) software were used for this process. Currently, 36 foci have been reported within the inferior frontal region, with 25 in the trigeminal part, nine in the orbital part, and two in the opercular part of the IFG. The anterior-inferior part of the left IFG is believed to play a significant role in integrating words into meaningful sentences (Badre & Wagner, 2007; Bookheimer, 2002; Menenti, Petersson, Scheeringa, & Hagoort, 2009). This activation might reflect elevated cognitive demands required to integrate non-literal meanings, as opposed to literal ones, into a sentence context (Bambini, Gentili, Ricciardi, Bertinetto, & Pietrini, 2011; Rapp et al., 2004; Rapp et al., 2007; Rapp et al., 2011). This region is, however, also involved when two-word metaphors instead of sentences are used as stimuli, so it certainly does not reflect sentence context integration alone (Lee & Dapretto, 2006; Mashal et al., 2007; Mashal et al., 2013). Other possible roles for the left IFG in understanding metaphors are meaning selection and evaluation, since a distinction must be made whether a word is intended metaphorically or literally. Research on literal language suggests that Brodmann area (BA) 45/47 may regulate the selection of multiple competing responses during sentence comprehension (Petrides, 2005; Rapp et al., 2012; Turken & Dronkers, 2011). We recently argued (Rapp et al., 2012) that reciprocal interactions between BA 47

Table 28.3 Activation likelihood estimation (ALE) meta-analysis of functional magnetic resonance imaging (fMRI) studies with idioms (idiom > literal, whole brain analysis).

Cluster	Hemisphere	Region	Brodmann Area	*x*	*y*	*z*	Volume (mm^3)
1	LH	Inferior frontal gyrus	45	−52	26	0	4,392
	LH	Inferior frontal gyrus	46	−48	30	8	
	LH	Inferior frontal gyrus	9	−52	24	18	
	LH	Inferior frontal gyrus	9	−54	16	24	
	LH	Inferior frontal gyrus	44	−50	18	16	
	LH	Inferior frontal gyrus	44	−58	14	14	
2	LH	Middle temporal gyrus	21	−60	−58	4	448
3	RH	Precuneus	7	16	−72	48	272
4	LH	Fusiform gyrus	20	−38	−10	−28	224
	LH	Parahippocampal gyrus		−36	−10	−24	

and the left middle temporal gyrus (Turken & Dronkers, 2011) might contribute to the selection between literal and non-literal meanings. Another possible role for the left IFG is the integration of world knowledge into a context (Rapp et al., 2011; Rapp et al., 2012), and that lower cloze probability of metaphoric stimuli (Rapp et al., 2004; Schneider et al., 2014) contributes to activation.

Another significant area in the meta-analysis is the left superior temporal gyrus. This brain region is located near Wernicke's speech area and maintains anatomical connections to numerous other semantic association centers (Turken & Dronkers, 2011), like BA 45/47 (Bahlmann, Mueller, Makuuchi, & Friederici, 2011; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011), to the more posterior superior part of the left inferior frontal gyrus (Broca's area) (Weiller et al., 2011), to other parts of the left lateral prefrontal cortex including Brodmann areas 6 and 46 (Turken & Dronkers, 2011; Weiller et al., 2011) and to the inferior parietal lobule (BA 39) (Turken & Dronkers, 2011). Recent research combining high temporal resolution imaging procedures with imaging methods in metaphor comprehension highlights a temporally early role in posterior brain regions (Schneider et al., 2014; Schneider et al., 2015). The left middle and superior temporal gyri may play such a role. A key role for this brain area in understanding non-literal language is compatible with lesion studies (Gagnon, Goulet, Giroux, & Joanette, 2003; Winner & Gardner, 1977). Further analysis of functional connectivity fMRI in this region would be quite interesting, especially since the first such study found sufficient evidence for such involvement (Mashal, Faust, & Hendler, 2005). The possible functional role also includes the setting up of cohesion

(Ferstl, Neumann, Bogler, & von Cramon, 2008; Rapp et al., 2012), a function that can be attributed not only to the left hemisphere (LH), but also to the right hemisphere (RH) homologue (e.g., Burgess & Chiarello, 1996; Kircher, Brammer, Tous Andreu, Williams, & McGuire, 2001; Mashal et al., 2005). With only 23% of the reported foci (60 foci reported in the literature are in the temporal lobe, 14 of them in the RH), the temporal lobe has the least pronounced left lateralization. In particular, the frontal lobes (35% of the reported foci) and the sub-lobar regions (33% of reported foci) have higher values. However, we must again emphasize that this type of analysis is not qualified to itemize the functional significance of reported foci. For example, functional connectivity analyses with Hebrew two-word metaphors (Mashal et al., 2005) indicate that the role of the right hemisphere homologue is substantial. The role of task instruction in fMRI has probably been investigated too little, since lesion studies indicate that the role of the right hemisphere homologue is critically dependent upon task instruction (Rapp, 2012; Rinaldi, Marangolo, & Baldassarri, 2004; Winner & Gardner, 1977).

Another significant cluster of the meta-analysis can be found in the left parahippocampal gyrus. This brain region has received minor attention in the lesion studies. Foci from Yang, Edens, Simpson, and Krawczyk (2009) and Forgacs et al. (2012) contribute most to the significance of this cluster in this ALE-analysis, but activations in the left hemisphere parahippocampus are also reported by others (Citron & Goldberg, 2014; Desai et al., 2013; Diaz, Barrett, & Hogstrom, 2011; Mashal et al., 2005; Mashal et al., 2013; Schmidt & Seger, 2009). It further plays a role in processing other types of non-literal language like irony (Akimoto et al., 2014) and idioms (Desai et al., 2013). Despite an apparent robustness of activations, the role of the parahippocampus has previously been discussed very little (see Rapp et al., 2012). The parahippocampal gyrus is part of the limbic system and contributes to linguistic ambiguity resolution on the sentence level (Hoenig & Scheef, 2005; Schmolck, Stefanacci, & Squire, 2000; Snijders et al., 2009), which could well explain its functional role. However, the brain region has multimodal functions (Aminoff, Kveraga, & Bar, 2013), and the parahippocampal gyrus may also contribute to contextual or emotion processing.

It is interesting to note that clinical populations, such as patients with schizophrenia, show activation differences in the left parahippocampal gyrus during the processing of metaphors (Mashal et al., 2013) and irony (Rapp et al., 2013). Although not significant in our meta-analysis, the right parahippocampal gyrus is also utilized during the processing of non-literal language. For example, it is activated when metaphors are produced (Benedek et al., 2014). On the basis of their meta-analysis, Yang and Shu (2016) suggested that the parahippocampal gyrus is used in the simulation of spatial information (see also Grill-Spector & Weiner, 2014). Proverbio et al. (2009) noted that it could be responsible for "providing emotional connotation" during non-literal language comprehension. The parahippocampal gyrus has extensive anatomical crosslinks to the aforementioned regions, such as the left IFG/BA 47 (Petrides, 2005), and functional connectivity to Wernicke's area has been shown using fMRI (Mashal et al., 2005).

Entrenched in linguistic literature is the idea that thinking processes include embodiment as a central element (Gallese & Lakoff, 2005; Lakoff, 2014; Lakoff & Johnson, 2008). The idea is that fictive motion is grounded in the sensorimotor system (Zhong & Liljenquist, 2006). What has received much attention recently is the involvement of the motor cortices and brain regions presumably associated with embodiment. Currently, the topic remains controversial in studies of non-literal as well as literal language (de Zubicaray, Arciuli, & McMahon, 2013; Watson, Cardillo, Ianni, & Chatterjee, 2013). However, there is an increasing number of studies concentrating on the use of metaphors (Aziz-Zadeh, Wilson, Rizzolatti, & Iacoboni, 2006; Chen, Widick, & Chatterjee, 2008; Desai et al., 2013; Romero Lauro et al., 2013) and idioms (Boulenger, Hauk, & Pulvermueller, 2009; Desai et al., 2013; Raposo et al., 2009; Schuil, Smits, & Zwaan, 2013). Several studies have demonstrated activation in the motor cortices during the processing of metaphors. A meta-analysis conducted by Yang and Shu (2016) used fictive motion sentences (such as "the road runs along the coast") and metaphoric actions. Fictive motion sentences contain a word that describes motion (in this case, "runs"), and regions for spatial encoding and recognition were expected in their meta-analysis, which were indeed found. However, this type of metaphor did not exhibit activation in the left premotor cortex. Fictive motion sentences bring together the concepts of conceptual metaphors and embodiment. Perhaps the right parahippocampal gyrus is involved in simulating information spatially (Bellmund, Deuker, Schroder, & Doeller, 2016; Benoit & Schacter, 2015). Seen separately, but also grounded in the notion of embodied cognition, are metaphoric action sentences (such as "grasp the idea"). These sentences are sometimes said to activate the premotor and motor cortices, and are often used to describe mental states (for example, "Matilde throws her sadness far away"; Romero Lauro et al., 2013). Some studies aimed to find a "somatotopy" for action metaphors, proverbs, and disentangled activation for "upper and lower limb metaphors." Yang and Shu (2016) found that metaphoric action lateralized to the left. However, some studies included negative findings. Aziz-Zadeh et al. (2006) studied the comprehension of metaphor and literal phrases containing hand, mouth, and foot action verbs. Their results showed that within the premotor cortex in the left hemisphere, a somatotopic activation pattern was found for literal phrases but not for metaphoric phrases. From that perspective, it would be logical to expect that regions of higher-order action intention (such as the inferior parietal lobule; Sowden & Catmur, 2015) also play a role in figurative language comprehension. For example, in the metaphor "to grasp the idea," knowing the intention of the action grasp (i.e., to get something that is needed) might be important for assessing the figurative meaning (i.e., to understand the idea).

Figure 28.1 demonstrates that the network involved for metaphor comprehension is not limited to the regions described (see Rapp et al., 2012, and Rapp, 2013, for further discussion of other brain regions involved). Other participating regions are the left superior fontal gyrus (with a speculative role in the uncertainty dissolve; Bach & Dolan, 2012), the medial prefrontal cortex (perhaps for suppression of the literal meaning; Cacciari & Papagno, 2012; Papagno & Romero-Lauro, 2010), the temporoparietal junction (for semantic and context integration), the cerebellum (which has a proven function in non-literal language comprehension; Cook, Murdoch, Cahill, & Whelan, 2004; Murdoch, 2010; Rapp et al., 2012), the precuneus (perhaps for mental imagery; Mashal, Vishne, & Laor, 2014), and the thalamus (suggested for identifying attributive categories and establishing semantic associations; Stringaris, Medford, Giampietro, Brammer, & David, 2007; or for ambiguity resolution; Uchiyama et al., 2012).

Brain Correlates of Idiom Processing

The next section of this chapter is on brain processing of idioms. Unlike metaphors, idioms have a unique meaning. Several definitions exist for idioms (Nunberg, Sag, & Wasow, 1994); idioms are a type of non-literal language; however—in contrast to metaphors—they do not necessarily have a wrong literal meaning.[1] It is prevalently assumed that idiomatic meaning, assumed unlike metaphoric meaning, is stored in the semantic memory as fixed "multiword strings," like other multiword strings, such as lines of poetry and popular song titles (Cacciari & Papagno, 2012). It has been assumed that such multiword strings may be stored as one unit in semantic memory. Consequently, in a recent overview on hemispheric processing of idioms, Cacciari and Papagno argue that the cognitive processes for the two may differ: "Metaphors have to do with categorization processes, while idioms have to do with retrieval from semantic memory" (Cacciari & Papagno, 2012, p. 370). A practical definition for research on their neuroanatomy is stated by Cacciari and Papagno (2012, p. 369): "Idiomatic is a fixed string of constituents whose meaning is not necessarily derived from that of its constituents." Further, because of the fixed meaning, one cannot suddenly "invent" an idiom, while this is possible for metaphors. The discussion of which are more frequent in everyday speech samples is ongoing.

A systematic search of the present literature yielded 11 fMRI studies on idioms and one for proverbs, which is lower than the number of studies on brain lesions and idioms (14).

Table 28.1 lists the fMRI studies. The first study was published in 2007 (Zempleni et al., 2007) and used Dutch idioms. The main finding of both studies was bilateral activation in the IFG and middle temporal gyrus for idioms > literal sentences. The reverse contrast (literal > figurative) also showed bilateral activations. Zempleni also investigated a small number of patients with schizophrenia and found aberrant activation in them (Zempleni et al., 2006).

In 2008, three studies were published. In a study on Hebrew, Mashal et al. (Mashal, Faust, Hendler, & Jung-Beeman, 2008) investigated comprehension of idioms. Their main findings were that brain activation for comprehension of the (correct) figurative meaning of the idiom not only contrasted that for comprehension of literal control sentences, but also differed from that for processing the literal meaning of the idiom. The paper showed literal interpretation of idioms was associated with "increased activity in right brain regions including the right precuneus, right middle frontal gyrus

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[1] For example, the idiom "it takes two to tango" has a literally correct meaning.

(MFG), right posterior middle temporal gyrus (MTG), and right anterior superior temporal gyrus" (p. 848).

Lauro, Tettamanti, Cappa, and Papagno (2008) investigated the comprehension of idioms versus that of literal sentences in Italian. Their participants performed a picture-matching task, a task type that is often used in brain lesion studies. They also applied a dynamic causal modelling (DCM) analysis. Again, bilateral inferior frontal and right temporal activation were found. In addition, in accordance with previous findings, the opposite contrast activates right temporal regions.

The first study on English idioms was published by Boulenger et al. (2009), who investigated the role of the motor system in idiom comprehension. Again, left IFG activation was observed. In contrast to previous studies, no right cerebral activation was found. In a study from the United Kingdom, Raposo et al. (2009) investigated idiomatic action sentences. Although they included 56 stimuli and 22 participants, no contrast for idiomatic > literal sentences was detectable in this study. The study with the highest number of subjects (n = 37) (Kana, Murdaugh, Wolfe, & Kumar, 2012) also yielded a negative result. In this study, no activation was detected in the direct comparison between idioms > literal sentences; instead, the opposite contrast showed several activation clusters, mainly in the right hemisphere.

Another English-language study (Hillert & Buracas, 2009) used two types of idiomatic expressions, explicit and implicit, and compared them with literal sentences. Explicit idiomatic sentences activated the left IFG, while the contrast ambiguous idiomatic sentences > literal showed activation mainly in the medial prefrontal regions.

In a recent study with Chinese idioms, (Yang et al., 2016) investigated both opaque and transparent idioms. While opaque idioms activated left hemisphere limbic and right hemisphere temporoparietal regions, transparent idioms elicited only activation of the left hemisphere.

Two studies investigated both idioms and metaphors (Desai et al., 2013; Romero Lauro et al., 2013) and provided evidence for differences in brain processing between idioms and metaphors. Desai et al. (2013) reported differential activation in temporal and posterior brain regions, but less in the prefrontal regions.

The studies available on idiom comprehension offer the possibility of a coordinate-based meta-analysis. However, the current follow-up analysis, like the previous one (Rapp et al., 2012), has the severe limitation of having a very low number of reported foci. The 12 published studies report 74 exploitable foci from 265 participants, 48 foci in the left hemisphere and 25 in the right hemisphere. Schuil et al. (2013) reported only one focus in the midline posterior cingulate. Figure 28.2 shows their projections onto a brain surface. A meta-analysis (GingerALE 2.5, liberal threshold of 0.001 uncorrected, chosen minimum cluster size = 100 mm^3; see table 28.3) showed significant clusters in the left BA 45, left middle temporal gyrus, precuneus, and left hemisphere parahippocampal gyrus. Numerous studies reported left inferior frontal gyrus activation (Boulenger et al., 2009; Fernandino et al., 2013; Hillert & Buracas, 2009; Lauro et al., 2008; Mashal et al., 2008; Romero Lauro et al., 2013; Zempleni, Haverkort, Renken, & Stowe, 2007; Zempleni et al., 2006). The number of reported foci in the temporal lobes is equal for both hemispheres

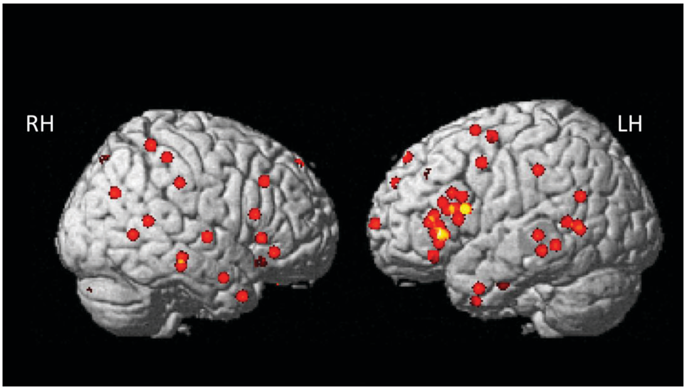

FIGURE 28.2. Projection onto a brain surface: foci for fMRI-activation idioms > literal stimuli. The 12 published studies report 74 exploitable foci from 265 study subjects, 48 foci in the left hemisphere and 25 in the right hemisphere.

(eight each), but more spatially distinct in the right hemisphere (see Rapp et al., 2012, for a discussion on this topic). Altogether, coordinate-based analysis clearly indicates that both hemispheres contribute to idiom processing.

Worth mentioning is the role of the medial prefrontal cortex in idiom comprehension, which is also supported by brain lesion research (Cacciari & Papagno, 2012; Cacciari et al., 2006; Papagno & Caporali, 2007; Papagno, Curti, Rizzo, Crippa, & Colombo, 2006, Papagno, Tabossi, Colombo, & Zampetti, 2004). According to the model of idiom comprehension put forward by Papagno and Lauro (Lauro et al., 2008; Papagno & Romero-Lauro, 2010), the medial prefrontal regions are responsible for response monitoring during idiom comprehension and suppression of alternative (literal) interpretations. Beyond that, "theory of mind" is essential for the comprehension of many non-literal stimuli, so that the medial prefrontal contribution to theory of mind (Amodio & Frith, 2006) also represents a functional role for this brain region. Contributions from the medial prefrontal cortex are also found in other types of non-literal language, such as irony (see Rapp et al., 2010, for review), metonymy (Rapp et al., 2011), and metaphors (Subramaniam et al., 2013).

IMPLICATIONS FOR FURTHER RESEARCH

Although knowledge and data have substantially increased during the past few years, several issues make further research worthwhile. One field is the developmental perspective. Metaphor comprehension has a rather late developmental biology continuing during childhood (Nippold & Taylor, 1995; Nippold, Uhden, & Schwarz, 1997), so from its timing it possibly interrelates with critical maturation and lateralization processes, which has been postulated to be of interest for understanding impairment in diseases (Sakai, 2005; Sommer & Kahn, 2009). To better understand the functional neuroanatomy, further studies on the interplay between brain regions (e.g., connectivity analyses) are worthwhile. The same is true for a more integrative perspective from fMRI to comprehensive research using techniques with better temporal resolution. It is now possible, for example, to combine electrophysiology and blood oxygenation level dependent (BOLD)–based techniques (Schneider et al., 2014), or fMRI and eye-movement tracking (Bonhage, Mueller, Friederici, & Fiebach, 2015). However, in the case of idioms and metaphors, such combinations are only in their infancy. fMRI research in clinical populations, such as patients with schizophrenia, is increasing (Kircher et al., 2007; Mashal et al., 2013; Mashal et al., 2014; Schneider et al., 2015), while autism and other diseases are less well studied. Metaphor aptness (Chiappe, Kennedy, & Smykowski, 2003; Giora, 2002) and personality traits (Rapp et al., 2010) have also been studied very little using today´s imaging research techniques.

Emotion (see van Berkum, Chapter 29 in this volume) is a potential factor in the process of understanding the neural correlates of metaphors (Citron & Goldberg, 2014; Kövecses, 2003; Mirous & Beeman, 2012), as metaphors are often used to express emotional content (Fainsilber & Ortony, 1987; Gibbs & Leggitt, 2002). Metaphors showed different fMRI activation in an emotional valuation paradigm than in a metaphoricity judgment paradigm in our previous study (Rapp et al., 2007), while there were no differences found between emotionally positive and negative metaphors (unpublished data). In contrast, Forgacs et al. (2014) found a stronger activation of emotionally negative-colored metaphors in the same brain region. Overall, emotional content in the more recent studies seems to attract more consideration. A comprehensive fMRI study (Subramaniam et al., 2013) examined the effects of the emotional content of metaphors on brain activation. These confirmed a specific role of the left IFG. The medial prefrontal cortex seems to play an important role in affect recognition during metaphor comprehension. The authors suggested a connection with processes of cognitive control processes (Subramaniam et al., 2013). In a recently published study, Samur et al. (2015) showed that the emotional context in metaphorical interpretation of a sentence affected brain activation in the areas of movement (visual motion areas).

It is always subjective to suggest what research needs to address most urgently, but a rather neglected area is the explanation of brain activation for literal sentences > metaphors. Recall that metaphors, even novel ones, are not necessarily more difficult to process and do not necessarily require longer reaction times (Blasko & Connine, 1993; Glucksberg, 2003). There is frequently reported activation for literal > non-literal stimuli in fMRI investigations, but it is rarely discussed. To use idioms as an example, all nine studies analyzed the contrast for literal > idiomatic stimuli (Figure 28.3); however, only Boulenger et al. (2009) and Yang et al. (2016) reported a negative result.

For example, Kana et al. (2012) reported, "Idiomatic sentences showed greater activation in the left fusiform gyrus, right parahippocampal gyrus, bilateral STG, LMTG, and RMFG" (p. 20). All the other studies reported the coordinates of their results; these studies together reported 54 foci, which is a comparable magnitude to the foci reported in the "other direction." Their projection onto a brain surface is shown in Figure 28.3,

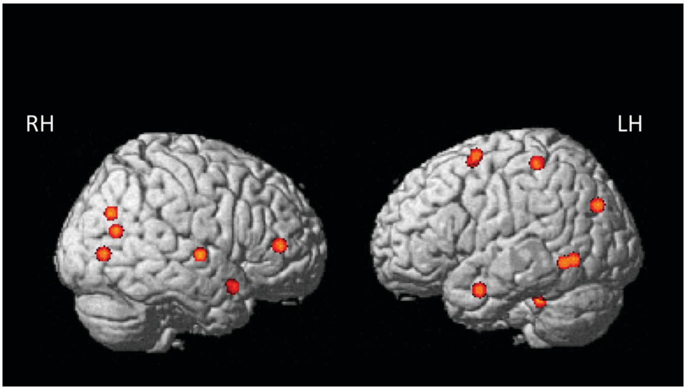

FIGURE 28.3. Projection onto a brain surface: 37 foci reported in 8 studies for differential contrasts literal stimuli > idioms.

and makes clear that they are not restricted to areas classically attributed to deactivation phenomena. It is still a question for further research to offer a better explanation.

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CHAPTER 29

LANGUAGE COMPREHENSION AND EMOTION

Where Are the Interfaces, and Who Cares?

JOS J. A. VAN BERKUM

INTRODUCTION

WHEN you hear somebody speak, or read a bit of text, you are somehow assigning meaning to an unfolding sequence of signs. Because of the representational and computational complexity involved, this process of language interpretation is considered to be one of the major feats of human cognition. However, you also happen to be just another mammal, and as such, you are biologically predisposed to have emotions, evaluations, and moods (i.e., to *feel* certain things about your environment). How do these two acts of assigning meaning relate to one another? And what are the implications for neurolinguistics, the endeavor to understand how the brain realizes language use? These are the central questions addressed in this chapter.

Over the last few decades, interest in the role of emotion in cognition has sharply increased, and a substantial part of current cognitive neuroscience research is about how affective factors mesh with cognition. With some delay, this affective turn in research on mind and brain has also reached the language sciences (e.g., Corver, 2014; Jensen, 2014; Majid, 2012; Peräkylä & Sorjonen, 2012; Van Berkum, 2010). In neurolinguistics, for example, an older strand of research on the processing of emotional prosody (e.g., Pell, 1999) is now joined by research on such topics as the impact of emotional state on language comprehension (e.g., Egidi & Carramazza, 2014; Van Berkum, De Goede, Van Alphen, Mulder, & Kerstholt, 2013), the processing of "emotion words and sentences" (e.g., Hoffmann, Mothes-Lasch, Miltner, & Straube, 2015; Ponz, Montant, Liegeois-Chauvel, Silva, Braun, Jacobs, & Ziegler, 2014), and the brain's response to swear words and other morally loaded language (Leuthold, Kunkel, Mackenzie, & Filik, 2015; Van Berkum, Holleman, Nieuwland, Otten, & Murre, 2009).

But what is the status of such research in the language sciences? When discussing such work with students in linguistics programs, the response is often mixed, in a way that may well be indicative of a wider attitude in the field. Many find the topics quite interesting. Emotion is "catchy," and discussing its interface with language sometimes offers a welcome change from such topics as predicate logic, minimalist syntax, or combinatorial symbol processing in the brain. Also, many phenomena are saliently connected to the students' personal lives, from the reduced effectiveness of using a non-native swear word to the painful sting of sarcastic prosody or a hesitant reply. At the same time, these students often feel that research on language and emotion is not really "at the heart of the matter." The reasoning seems to be something like this:

1. Language is a code via which we communicate about *everything*, from muffin recipes to our deepest fears, for a principally infinite number of reasons, and to a principally unlimited number of effects.
2. Psycholinguistics and the associated cognitive neuroscience research endeavor should study the generic mechanisms via which people acquire and use that code.
3. *Other* disciplines, like emotion science or social psychology, should study what happens when people communicate about the specific things they do, and why they choose to do so.
4. Although psycholinguistics is connected to those other disciplines in virtue of people using language for everything, there is nothing about the interface that is really of relevance to the task of understanding the *generic* mechanisms via which people acquire and use language.

The reasoning is intuitively compelling, for muffin recipes, but also for our fears and other emotions. Indeed, if human emotion is just a topic, a cause, or a consequence of particular instances of language use, cleanly separated from the machinery that does the language processing, psycholinguistics can just focus on the processing *regardless of emotion*. So, is it this simple? In this chapter, I argue that it is not. The processing of language and emotion is intricately intertwined, in ways that psycholinguistics and the associated cognitive neuroscience enterprise cannot afford to ignore.

The analysis begins by examining why emotion is not naturally foregrounded in language processing research. Because many readers will not be familiar with current views on emotion, I subsequently review some basic insights, covering short-lived salient emotions as well as other affective phenomena. After that, I make explicit the various types of representations that people compute as they use language, ask where emotion might kick in, and apply the resulting *Affective Language Comprehension* model to several neurolinguistics studies—this is the heart of the chapter. Finally, I explore how the model can contribute to neurolinguistics and other fields.[1]

A terminological note: just as in emotion science, I will use "emotion" in two different ways in this chapter. The narrow meaning is that of the event-driven short-lived phenomena that immediately come to mind when thinking about emotion: fear, joy, anger, pride, disgust, and so on. More broadly construed, the term "emotion" (or "affect") covers emotions in this narrow sense, but also other affective phenomena, such as affective evaluations and moods. Definitions of these various phenomena will be given later in the chapter.

The Standard Approach to Language Processing

Attention to emotion in psycholinguistics and the associated cognitive neuroscience research is relatively recent, and current major textbooks and handbooks still reveal a thoroughly "cold," non-affective perspective on language processing that has characterized the field for decades. The roots of this cold perspective can be found in several important historical developments in the field, each of which led to a particular bias (see van Berkum, 2018, for more extensive discussion).

Technological Systems Focus

Just like other disciplines within, or overlapping with, cognitive psychology, psycholinguistics has been heavily shaped by the technology-driven digital information processing perspective in that larger field. In psycholinguistics, this technology frame has inspired people to ask about such things as how comprehenders decode noisy acoustic signals, store and retrieve lexical representations, recover syntactic structure, derive a proposition, compute reference, update the situation model, and code their own ideas for subsequent transmission—all questions about retrieving, manipulating, and storing information. As might be expected, though, the technology frame did not readily lead to questions about emotions, evaluations, and moods, or the needs of real living organisms that give rise to these affective phenomena.

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[1] This chapter has overlap with Van Berkum (2018), particularly in the second and third sections. However, while in the latter paper, I explore the interfaces between language and emotion with swear words and present a model-driven discussion of the multifaceted nature of word valence, the current chapter has a somewhat stronger cognitive neuroscience orientation, discusses a wider range of examples, and applies the proposed model to specific neurolinguistics studies.

Code-Cracking Focus

Psycholinguists have always enjoyed the luxury of being able to work from whatever linguists had discovered about the nature of language. But with that luxury also came subject matter biases operating in linguistics itself. Mainstream linguistics in the 1970s–1990s focused on language as a generative coding system, and abstracted away from actual usage. As such, it has inspired a lot of psycholinguistic research on how people crack the linguistic code (cf. all the research on lexical retrieval, syntactic parsing, anaphoric reference, and ambiguity resolution) and how they acquire or lose their code-cracking competence, but it has *not* inspired psycholinguists to study how the code actually gets to *affect* people.

Modularity Focus

Third, even for psycholinguists who did acknowledge the importance of emotion to mental life, nothing of importance seemed to follow for their everyday scientific concerns. After all, was the language system, or at least the most interesting bit of it, not "informationally encapsulated" from the rest of mental life anyway? The idea that language was an independent "module" in the mind (Fodor, 1983) paved the way for thinking about language comprehension as computing what is said and implied *before, and cleanly separate from*, computing the affective significance for the reader or listener.

Uniqueness Focus

As scientists carve up the world between them, it is only natural that people in different disciplines tend to focus on what is unique to "their" chunk of the world. Language is a discrete combinatorial system for very precise reference, unique in the animal kingdom. However, psycholinguistics cannot focus only on the unique. To understand how the system actually works in practice, you also need to look at the parts that may *not* be so unique for Homo sapiens, but are critical just the same—such as memory, or emotion. For example, although the observation that learning principles studied by behaviorists could not easily account for the complexity of linguistic behavior was critical in the development of the language sciences, this observation does *not* imply that as language users, people are free from the standard effects of classic emotional conditioning.

The previously mentioned biases are to a large degree responsible for the dominant, standard perspective on language use in psycho- and neurolinguistics, a perspective one might call the *TCP/IP approach to language use*. In the TCP/IP approach, language users are reduced to computational devices that exchange information via a fixed communication protocol (a human TCP/IP[2]), coding ideas into utterances and transmitting them for subsequent decoding at the other end, with the conversion to or from the code carried out by special language “modems.” The research agenda of this approach can be extracted from any recent psycholinguistics textbook or handbook, as well as from programs of major psycho- or neurolinguistics conferences. Most of that agenda is about storing, retrieving, manipulating, and transmitting data, about how listeners figure out the bits of information that speakers want to pass on to them, and about how speakers figure out what listeners already know, so that fewer bits need to be coded and transferred.

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[2] TCP/IP is a communication protocol that regulates information exchange between computers

Now, human language *is* a code for communication, and language users *do* need to master that code to be able to profit from the additional precision and expressivity that language provides. Research on the nature of the code, and on how language users acquire, crack, and generate bits of this code, is therefore crucial to understanding the human mind and brain. Having said that, it is clear that the TCP/IP approach cannot be the whole story. Most obviously, language users are *not* dispassionate, immobile information systems representing and exchanging information; they are animals with things at stake, and with situations to cherish or best avoid. They *care* about things. Moreover, they care enough about things to want to use language to inform, manipulate, or deeply connect with other people (cf. Tomasello, 2008). They *do* things with words (Austin, 1962), to each other, and sometimes also to themselves. Emotion is at the heart of all that. Hence, if we really want to understand the neural mechanisms that allow language to be *useful*, we need to ask about emotion.

WHAT IS EMOTION? A PRIMER FOR LANGUAGE RESEARCHERS

Emotion is what has kept you alive so far—although details may vary, emotion may have saved you from drowning, being run over by a car, losing sight of your primary caretakers in a large crowd, or losing the means to sustain yourself. The affective systems responsible for emotions, evaluations, and moods are at the core of how brains control adaptive behavior in a complex environment (Damasio, 1994; Davidson, 2012; Frijda, 2008; Ledoux, 1996; Panksepp & Biven, 2012; Scherer, 2005)—not just in humans, but in all mammals. Emotion science is a huge area of research, with branches reaching into such disciplines as evolutionary biology, neuroscience, psychology, ethnography, and philosophy (for various broad displays of this vast area, see Barrett, Lewis, & Haviland-Jones, 2016; Davidson, 2012; Nussbaum, 2003; Prinz, 2004; Sander & Scherer, 2009; Wetherell, 2012). There are countless fundamental debates, on such things as what counts as emotion, on whether we have basic emotions, on the relative contribution of biology and culture, and on how emotion relates to cognition (see Barrett et al., 2016, for an extensive overview). Here, I focus on several key ideas and distinctions that have generally proved useful to the field and are important when addressing the relation between emotion and language.

The starting point is a working definition of emotion that is suitable for current purposes:

> An emotion is a package of relatively reflex-like synchronized motivational, physiological, cognitive, and behavioral changes, triggered by the appraisal of an external or internal stimulus event as relevant to the interests (concerns, needs, values) of the organism, and aimed at generating a prioritized functional response to that stimulus event. The changes involved need not emerge in consciousness, but to the extent that they do, they give rise to feeling.

This definition (which largely follows Scherer, 2005, but also incorporates aspects of other proposals, notably Adolphs, 2017; Damasio, 2010; Frijda, 2008; Lazarus, 1991; Panksepp & Biven, 2012), highlights several core properties of emotion that I will unpack in the following.

(1) *Emotions are triggered by the appraisal of something as relevant to our concerns.* Emotions emerge when something about a stimulus is appraised as relevant to one's interests, either positively (such as when you win a contest, or see your child do well in a school performance), or negatively (such as when you are insulted, find a huge spider in the crib of your two-month-old baby, or drop your smartphone on the floor). An emotion is referential (i.e., *about* something). What it is about might be "out there," as in all the preceding examples, or inside your head, as when you remember or imagine any of the preceding, or mentally represent these scenarios in response to language; that is, although examples in the emotion literature are often about concrete events, objects, or situations in our environment, *thoughts* (consciously as well as unconsciously entertained) can just as easily trigger emotion. Following Damasio (2010), I will use the term *emotionally competent stimulus*, or ECS, to cover all of this. Appraisal can to some extent be deliberate (i.e., under slow conscious control), but in line with what emotion is supposed to do for us, it is usually fast, automatic, and unconscious (Adolphs, 2017; Frijda, 2008; Prinz, 2004; Scherer, 2005; Zajonc, 1980)—as every psychotherapist or coach will know, people often don't know what aspect of a situation, person, or event exactly triggered their emotion, or for what reason. Also, as illustrated by research on olfactory and visual perception (e.g., Li, Moallem, Paller, & Gottfried, 2007; Tamietto, Castelli, Vighetti, Perozzo, Geminiani, Weiskrantz, & de Gelder, 2009), people can respond affectively without having *consciously perceived* the stimulus at all.

(2) *Emotions involve a "package" of relatively automatic, short-lived, synchronized changes in multiple systems.* Emotion is not just about appraising something as relevant to your interests, but also about *doing* something about it. For example, when something makes you angry, your heart beats faster, you sweat a little more, and stress hormones are released, as your body is preparing itself for "combat." You will momentarily feel a

strong urge to act, and perhaps you will strike or yell at something, or someone. Your face will have an angry expression. Attentional focus will briefly narrow, such that you are no longer able to attend to other things in the environment. And finally, you may become very aware of all of this, giving you the typical "feel" of anger. These specific changes make up the average "package" for anger. Qualitatively different emotions, such as anger and fear, have different action packages, with some shared ingredients (e.g., both increase sweating), but also some major differences (e.g., in contrast to anger, fear increases the probability of retreat and avoidance). Specific instances of anger may also differ somewhat in their exact "mix" of ingredients, and some mixes will be more prototypical than others. The key observation, however, is that emotions involve relatively automatic, short-lived, and synchronized changes along several different dimensions: (a) *motivational changes* or *action tendencies*, the readiness to engage in, or disengage from, particular behavior; (b) *physiological changes* that prepare the body for action or impact; (c) *cognitive changes*, such as increased attention and better memorization; and (d) *behavioral changes*, involving approach or avoidance, as well as more specific actions such as smiling, frowning, shouting, crying, changing posture, stroking, exploring, or playing.

(3) *Emotions briefly take control.* Emotion emerges when something is deemed sufficiently important to relatively automatically engage multiple systems simultaneously, to have "all hands on deck." It is also about doing something *now*. Frijda (2008, p. 72) characterizes emotion as "event- or object-instigated states of action readiness with control precedence"; that is, you really have an urge to do something *right now*: strike out or yell at the intruder, or write that email *now*. And that makes sense; after all, emotions are designed to watch over your interests, directly or indirectly rooted in core biological values shaped by evolution. Although culturally conditioned and other personal life experiences construct additional layers of emotional complexity that are unique to humans (Barrett, 2014), emotion is first and foremost about "biological homeostasis," about regulating life within survival-promoting and agreeable ranges (Damasio, 2010; Panksepp & Biven, 2012). Emotions are bits of rapid biological intelligence that have proved useful in the past—reflex-like solutions to recurring problems in the life of the species (and its ancestors), briefly taking control, but also open to various forms of regulation (Adolphs, 2017).

(4) *Emotions are not necessarily conscious.* A crucial insight in emotion science is that emotion doesn't need to be conscious (Damasio, 2010; Frijda, 2008; Panksepp & Biven, 2012; Scherer, 2005); that is, one can have all of the ingredients (a) to (d) mentioned earlier without actually being aware of them (i.e., of *feeling* them). This may be counterintuitive, because in daily life we use "emotion" and "feeling" interchangeably. When *strong* emotions are elicited, we will certainly "feel" them. But what holds for other aspects of brain function also holds for emotion: most of the computations are done without us being aware of the process and its results (Adolphs, 2017); that is, weak emotions may unfold and affect our thoughts and behavior without *any* subjective awareness. If this is hard to imagine, think about moments in life when you suddenly became aware that you have been avoiding someone, or something, or that in particular

situations, your neck muscles tend to tighten up. Or about the effort that is sometimes needed to make the relevant appraisals involved in your emotional life explicit, so that you can reflect upon them.

(5) *Emotions have ancient triggers but can hook up to new ones via learning*. For psycholinguists, a particularly critical observation is that there seem to be no limits on the types of stimuli that can become emotionally competent. For a limited class of biologically significant stimuli (e.g., pain, an unexpected loud noise, signs of decay, being bodily restricted, the anticipation of sex or food, being stroked or otherwise cared for, the loss of social bonds, a helpless baby, and the basic emotional displays of conspecifics, such as smiles and frowns, aggression, or playful movement; Panksepp & Biven, 2012), that competence is simply hardwired into your brain. Via "emotional conditioning," however, an *infinite* number of other stimuli can also become emotionally competent (De Houwer, Thomas, & Baeyens, 2001; Hofman, De Houwer, Perugini, Baeyens, & Crombez, 2010; Ledoux, 1996; Panksepp & Biven, 2012), as generic categories, or as specific tokens. The amygdalae are believed to be crucial to such emotional conditioning, and they are capable of forging emotional associations without any awareness or episodic recollection of the coupling (Janak & Tye; 2015; Ledoux, 1996; Phelps, 2006). However, depending on the specific emotion involved, many other emotion-relevant neural systems can also be involved, as generators of the affective brain state (i.e., the *unconditioned response*, or UCR) that is now associatively connected with something new (the *conditioned stimulus*, or CS), but also by realizing brain states that enhance the formation of new memory (e.g., via arousal; Panksepp & Biven, 2012).

Crucially , as an unavoidable consequence of the generic mechanisms of associative learning in the brain, the *non-natural signs* studied by semiotics and linguistics (e.g., a brand logo, a word, a particular linguistic construction) can also become emotionally competent (e.g., Fritsch & Kuchinke, 2013; Hofmann et al., 2010; Jaanus, Defares, & Zwaan, 1990; Kuchinke, Fritsch, & Müller, 2015; Keuper, Zwanzger, Nordt, Eden, Laeger, Zwitserlood, Kissler, Junghöfer, & Dobel, 2014; Ortigue, Michel, Murray, Mohr, Carbonnel, & Landis, 2004; Pülvermüller, 2012; Schacht, Adler, Chen, Guo, & Sommer, 2012; Silva, Montant, Ponz, & Ziegler, 2012). Such conditioning occurs automatically whenever a particular sign is sufficiently reliably (or sufficiently strongly) paired with affective responses, either in *actual* experience, or when such experience is sufficiently imagined (as when we read a novel). Of course, the emotional conditioning process must always bootstrap from *something*. But as the advertisement industry shows, this is not hard at all: companies effectively associate their car, coffee, and ice cream brand names or logos with positive emotions, simply via systematically pairing the initially neutral stimulus with something that already *is* a highly competent ECS (e.g., an attractive man or woman, a scene with friendly people having fun). Although emotional conditioning can lead to the transfer of strong and very salient emotions (as with the fear conditioning that underlies PTSD or phobia), it usually affects us in much subtler ways, via sometimes fully unconscious affective evaluations and the associated preferences (see Hofmann et al., 2010, for a meta-analysis with verbal and nonverbal stimuli). In all, emotions are sticky little things, value-relevant response packages that can attach themselves to *anything* without you noticing, and with the appraisal that is needed to elicit them consisting of little more than the automatic retrieval of an acquired association from long-term memory.

(6) *Affective evaluation is low-intensity emotion.* In a wide variety of fields, ranging from social psychology (e.g., Zajonc, 1980) to the neuroscience of visual perception (e.g., Barrett & Bar, 2009), research has shown that we hardly ever see things in a neutral way: affective evaluation is part and parcel of how we perceive the world. In the words of Zajonc (1980, p. 154):

> One cannot be introduced to a person without experiencing some immediate feeling of attraction or repulsion and without gauging such feelings on the part of the other. [. . .] Nor is the presence of affect confined to social perception. [. . .] We do not just see "a house": we see "a handsome house," "an ugly house," or "a pretentious house." We do not just read an article on attitude change, on cognitive dissonance, or on herbicides. We read an "exciting" article on attitude change, an "important" article on cognitive dissonance, or a "trivial" article on herbicides. And the same goes for a sunset, a lightning flash, a flower, a dimple, a hangnail, a cockroach, the taste of quinine, Saumur, the color of earth in Umbria, the sound of traffic on 42nd Street, and equally for the sound of a 1,000-Hz tone and the sight of the letter Q.

Such automatic affective evaluations of the world around us build on the same affective systems that generate salient emotions like anger, fear, disgust, pride, or joy. With evaluation, however, the intensity of the emotion is so low that the response feels like a quality of the stimulus ("an ugly house"), rather than like a particular state that we are in ("that house made me feel disgusted"; see Barrett & Bar, 2009, for this distinction). Importantly, just like more salient emotions, evaluations have an action component (emphasized by the term "preference"): a more positive evaluation is associated with approach motivation, with—consciously or unconsciously—*preferring* the evaluated item over something else. Furthermore, these affective evaluations are by no means necessarily "*post*-perceptual," or "*post*-conceptual" (i.e., are not necessary generated only *after* something has been fully identified or conceptualized in cognitive terms). In vision, for example, affect can be part of the *initial* response to low-resolution, "coarse" aspects of an image, either because of some evolutionary hardwiring (e.g., jagged contours, or the outline of what might be a snake), or because of the associative conditioning brought about by real or vicarious experience (e.g., the contours of a gun; see Barrett & Bar, 2009). Echoing the classic psychological notion of subjective perception, there is growing evidence in cognitive neuroscience that what something *is* can often not be meaningfully separated from what it means *to me*—perceptions are not objective, and affect can be an intrinsic part of perception (Barrett & Bar, 2009; Gantman & Van Bavel, 2015; Lebrecht, Bar, Barrett, & Tarr, 2012).

(7) *Mood.* Mood differs from short-lived emotion in that it involves a relatively slow-changing affective background state that is not really *about* something (i.e., is not

"referential"; Forgas, 1995; Scherer, 2005). Also, whereas short-lived emotions play their role via unique prioritized action packages, mood is believed to play a functional role in signaling the amount of resources available for exploration of the environment (Zadra & Clore, 2011), and/or for signaling that the current course of action is working out well (Clore & Huntsinger, 2007). The effects of this show up in differential patterns of action *and* cognition. For example, in a bad mood we are not only less inclined to climb a steep hill, but also inclined to overestimate the steepness of that hill (Zadra & Clore, 2011). Furthermore, a bad mood narrows the spotlight of visual attention (Rowe, Hirsch, & Anderson, 2007), and reduces such things as the width of associative memory retrieval (Rowe et al., 2007), the use of scripts in episodic memory retrieval (Bless, Schwarz, Clore, Golisano, Rabe, & Wölk, 1996), or the sensitivity to social stereotypes in person judgment (Park & Banaji, 2000). In all, mood tunes cognitive processing in a variety of interesting ways, again without us being aware of it.

(8) *Emotions, evaluations, and moods recruit special neural circuity.* Emotion is important enough to warrant biologically evolved special neural and neuro-endocrine machinery, partially or fully emotion-dedicated systems that we share with many other animals (Adolphs, 2017; Panksepp & Biven, 2012; see also various chapters in Barrett et al., 2016, for review). Many of those are subcortical structures (e.g., amygdala, hypothalamus, nucleus accumbens, ventral tegmental area (VTA), periaqueductal grey (PAG)), but various regions of the neocortex (e.g., insula, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC)) are also involved. Some of the emotion-relevant neural structures are responsible for generating the physiological component of emotion (e.g., the hypothalamus, which controls much of the body's internal milieu via direct neural innervation, as well as a wide array of hormones released by the pituitary gland). Others play a crucial role in supporting the *subjective feeling* of an emotion, such as the anterior insula, which provides a map of visceral sensation (Craig, 2009), or the PAG, which has been argued to underlie aspects of subjective core affect (Panksepp & Biven, 2012; see also Satpute, Wager, Cohen-Adad, Bianciardi, Choi, Buhle, Wald, & Barrett, 2013). The degree to which *specific* emotions have their own dedicated, non-overlapping bits of the brain is heavily debated, and the most plausible model is one in which emotionally critical structures like the amygdala play a—potentially different—role in different emotions as a function of being recruited in a different wider network (Adolphs 2017; Hamann, 2012; Kragel & LaBar, 2016; Pessoa, 2017). In any case, careful cross-species studies of systems involved in fear, rage, care, or reward (reviewed in Panksepp & Biven, 2012) unequivocally show that nature did not leave emotion entirely up to chance.

(9) *The utility of emotion.* Our emotional life covers a vast range of phenomena, intense and subtle, consciously experienced or unconsciously nudging us, experienced as strong emotion "in us," or leading us to simply and sometimes imperceptibly "prefer" particular things—people, objects, signs, ideas, actions—over others, or to refrain from exploration at all. The point of all this, of course, is that our emotional life controls our behavior. Emotions and evaluations are "motive states" (Frijda, 2008, 2013), urging or

nudging us to approach or avoid, prefer, attend to, explore, grab, attack, submit to, care for, play with, or protect oneself from entities or events out there in the world, all because of how those entities or events relate to our interests (Damasio, 1994; Frijda, 2008; Panksepp & Biven, 2012). And emotion does so right here, in *your* life. Emotional control is *not* just something that was vital when humans were hunter-gatherers, and obsolete in this age of food counters, gadgets, and the Internet. The motive states that are part and parcel of emotions, evaluations, and moods control much of your everyday behavior, from the supermarket you go to and the things you buy there, to the people you seek out to chat and perhaps live with. They also determine whether you read on or whether you cast this chapter aside, and whether you mentally explore certain ideas or not. Emotions, evaluations, and moods need not be very strong to exert this control, and we may not be aware of how they tug at us at all; our decisions to pursue some things over others can be controlled by very subtle valence differences (cf. micro-valence; Lebrecht et al., 2012). But they do guide us in our actions.

Those actions can be overt behavior, but also *acts of thinking*. For example, emotions and evaluations play a crucial role in what we often experience as "rational" reasoning and decision-making (e.g., Bechara, 2009; Damasio, 1994; Gigerenzer, 2007; Phelps, Lempert, & Sokol-Hessner, 2014), when people are, for example, considering consumer products or medical treatments (Kahneman, 2011), or thinking about a morally responsible course of action (Greene, 2014; Haidt, 2012). Emotions and evaluations also influence attention (e.g., Harmon-Jones, Gable, & Price, 2012; Vuilleumier & Huang, 2009), memory encoding and retrieval (e.g., Adolphs, Denburg, & Tranel, 2001), and reasoning and decision-making (e.g., Damasio, 1994), and the specific beliefs that people are inclined to commit themselves to (Frijda, 2008) (for reviews, see Dolcos & Denkova, 2014; Dolcos, Iordan, & Dolcos, 2011; Pessoa, 2008, 2010; Phelps, 2006; Phelps et al., 2014; Zadra & Clore, 2011). Most of this affective control over our thinking occurs without our being aware of it.

Just like in other mammals, our affective system is thus key to the control of adaptive behavior in a complex environment (Panksepp & Biven, 2012). And just like other mammals, such control is greatly enhanced by our capability for associative and other forms of learning. What is special about us, Homo sapiens, is that our brain is capable of constructing a much wider and more diverse range of representations of that environment, as well as of ourselves, such that there is much more to have emotions *about* and evaluations *of*, and such that we can influence our and other people's behavior in much more sophisticated ways. At the pinnacle of that sophistication is our talent for language, and the inferential communication skills upon which that talent rests.

THE AFFECTIVE LANGUAGE COMPREHENSION MODEL

So, how does the affective control system that we have just examined mesh with language processing? In the context of this *Handbook*, it may seem obvious to address this question by (a) delineating the sets of neural structures involved in emotion and language processing, as well as the structural and functional connectivity between those sets; and/or (b) simply reviewing all the empirical cognitive neuroscience research (with electroencephalography [EEG], magnetoencephalography [MEG], functional magnetic resonance imaging [fMRI], etc.) on specific interactions between language and emotion and inductively infer generic insights from that. However, these are *not* the approaches taken here. As for the first, the set of neural structures involved in emotion is very large, and there is much debate on the precise functional characterization of those structures, as well as increasing awareness of the importance of dynamically configured networks and the different roles that a particular node can play as a function of the network it is in (Hamann, 2012; Pessoa, 2017). The same holds for language processing (see the many chapters in this *Handbook*). This makes the hypothesis space for a bottom-up connectivity-based approach rather large (but see Koelsch, Jacobs, Menninghaus, Liebal, Klann-Delius, von Scheve, & Gebauer, 2015).

As for the second approach, reviews of concrete cognitive neuroscience experiments that explore the interface between language and emotion are extremely useful (e.g., Citron, 2012). At the same time, I think they should be complemented by a theoretical perspective. As reflected in rather loosely used expressions like "emotion sentences," much of the cognitive neuroscience research on language and emotion operates with a relatively crude, non-articulated model of language processing—usually one that focuses on context-free lexical or sentence meaning, at the expense of context-dependent pragmatic levels of interpretation. If we are to make progress on how emotion and language processing interact, however, we must begin by honoring the *real* complexity of language processing. We know from pragmatics and psycholinguistics that language comprehension is a highly complex business that extends beyond the single utterance, involves several layers of interpretation, and is heavily context-dependent. We also know that language is just one of many simultaneous "channels" or sign systems via which we communicate, and that as we speak or write, such things as a flat voice, raising an eyebrow, a well-chosen emoji, or slightly turning away can make all the difference. What would be helpful is a wide-scope *functional* ("algorithm-level"; Marr, 1982) model that pulls these various things together, and that systematically explores the functional interfaces with emotion. A model like that can support researchers in orienting themselves, and in asking more refined questions about how language and emotion interface in the brain (see also Willems, 2011, for the importance of a top-down approach in cognitive neuroscience research).

In the remainder of this chapter, I describe and discuss such a blueprint for language comprehension: the *Affective Language Comprehension*, or ALC, model. The model was developed in a simple, two-step fashion, by first making explicit the various types of representations that listeners or readers compute as they process language, and by subsequently asking where emotion might kick in. The original description of the model (van Berkum, 2018) features an analysis of a verbal insult with a swear word, and provides a related ALC-based analysis of the concept of word valence. Here, I expand the scope of the model by showing that is also applies to several apparently much less "emotional" examples (see the following section), and by subsequently illustrating the utility of the model in interpreting the results of a few example cognitive neuroscience studies.

A Blueprint for Affective Language Comprehension

So what types of representations do language users compute when they comprehend a spoken or written utterance? Drawing upon central ideas in psycholinguistics and pragmatics (e.g., Clark, 1996; Enfield, 2013; Jackendoff, 2007; Kintsch, 1998; Levinson, 2006; Trueswell & Tanenhaus, 2005; Tomasello, 2008; Zwaan, 1999), as well as on what we know about representation and processing from cognitive science and neuroscience, Figure 29.1 represents a reasonable claim about the types of representation being computed and the subprocesses involved in computing them.

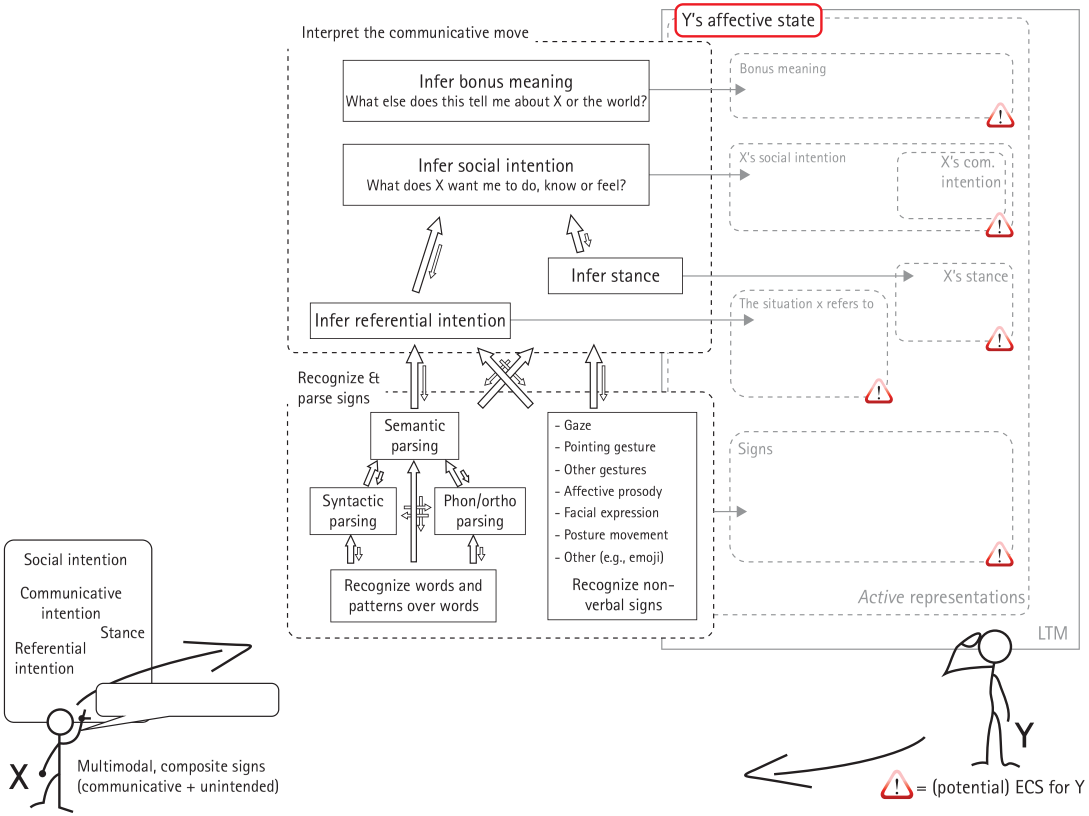
To see the model at work, I will discuss three different example utterances throughout: (1) a relative uttering, "Even *John* thinks euthanasia is acceptable in this case"; (2) a spouse uttering, "We've run out of dog food"; and (3) a teacher uttering, "The number 7 is *also* a prime number." The question I ask is: What impact can these communicative moves have on addressee Y at that point in the exchange? In particular, what representations might addressee Y compute, consciously as well as unconsciously, and which of those representations can in principle be emotionally competent stimuli (ECSs) for this addressee?

The Input: Multimodal, Composite Signs

In face-to-face conversation, conversational moves are always implemented as multimodal, composite signs, which include not just words arranged in a certain way, but a wide variety of nonverbal signs as well (Clark, 1996; Enfield, 2013; Goodwin, Cekaite, & Goodwin, 2012; Jensen, 2014). And in writing, people try to replace some of those signs (e.g., emoji, exclamation marks). As for our examples, speaker X will inevitably utter these sentences in a specific manner, such as with an annoyed, a pleading, or a relaxed and patient voice, and with a certain expression and posture—nonverbal aspects that, as will be seen in the following, are critical to interpretation.

Recognizing/Parsing the Signs Presented by the Speaker

The conventionalized ingredients of the composite sign will cue representations in long-term memory (LTM), traces of stable practices of sign use tracked by an ever-learning brain. For example, words like "euthanasia," "dog," or "number" will cue (retrieve, activate) whatever stable memory traces addressee Y has stored for those signs in the mental lexicon, including their phonological and/or orthographic form properties, their syntactic properties, and their conceptual properties, all of which will be brought to bear on how the sentence will be parsed (Jackendoff, 2007). Specific *constellations* of words, such as idiomatic expressions, or other stable constructions (Fillmore, Kay, & O'Connor, 1988; Lakoff, 1987), will likewise cue such representations in LTM (Jackendoff, 2007). And particular gestures, facial expressions, or emoji will do so as well.



Y's affective state
Interpret the communicative move
Infer bonus meaning
What else does this tell me about X or the world?
Infer social intention
What does X want me to do, know or feel?
Infer stance
Infer referential intention
Recognize & parse signs
Semantic parsing
Syntactic parsing
Phon/ortho parsing
Recognize words and patterns over words
- Gaze
- Pointing gesture
- Other gestures
- Affective prosody
- Facial expression
- Posture movement
- Other (e.g., emoji)
Recognize non-verbal signs
Bonus meaning
X's social intention
X's com. intention
X's stance
The situation x refers to
Signs
Active representations
LTM
Social intention
Communicative intention
Stance
Referential intention
X
Multimodal, composite signs (communicative + unintended)
Y
= (potential) ECS for Y

FIGURE 29.1. The *affective language comprehension* (ALC) model. Mental processes and the associated retrieved or computed representations are expanded for addressee Y only. Y's computational processes draw upon (and add to) long-term memory traces, and involve currently active dynamic representations that reflect what is currently retrieved from LTM, composed from elements thereof, and/or inferred from context, in response to the current communicative move. Y's active representations can be conscious or unconscious. Bonus meaning can be inferred from (or cued by) all other active dynamic representations, and Y's current affective state (e.g., mood) can influence all ongoing computational processes (arrows for these aspects not shown). The basic processing cascade is upward and incremental, starting from the signs, but small downward or sideways arrows between component processes indicate top-down or sideways prediction or constraint satisfaction. Within each of the delineated representational types, one or more ECSs can trigger an emotional processing cascade that affects Y's motivational inclinations, physiology, cognitive processing, and actual behavior, plus possibly Y's conscious feeling.

Abbreviations: ECS = emotionally competent stimulus; LTM = long-term memory; Phon/ortho parsing = phonological/orthographic parsing; X's com. intention = X's communicative intention.

Importantly, individual words and other "atomic" signs can *themselves* be ECSs, (i.e., trigger a bit of emotion *independent of the wider utterance and its pragmatic implications*). Models of how the brain represents word meaning have been shifting away from amodal feature lists and directed graphs, toward a more modal view in which lexical meaning is grounded in actual experience (e.g., Barsalou, 2008; Pülvermüller, 2012). Some psycho- and neurolinguists have begun to explore this for words that *refer* to emotions or evaluations and the associated behavior (e.g., "smile," "annoying"; Foroni & Semin, 2009; Künecke, Sommer, Schacht, & Palazova, 2015; 't Hart, Struiksma, Van Boxtel, & Van Berkum, 2018a, 2018b). But given what we know about associative learning in the brain, and of emotional conditioning as a special case of that (see previous discussion in this chapter), the potential for grounding lexical meaning in emotion is much wider than that (for evidence, see, e.g., Fritsch & Kuchinke, 2013; Hofmann et al., 2010; Jaanus et al., 1990; Kuchinke et al., 2015; Keuper et al., 2014; Ortigue et al., 2004; Pülvermüller, 2012; Schacht et al., 2012; Silva et al., 2012).

For example, if you have been raised with dogs, your personal concept "dog" will not just include how they (can and tend to) look, sound, smell, and feel when touched, but inevitably also how you relate to them affectively, with good or bad experiences leading to traces of positive or negative emotion, respectively. Growing up in an environment where euthanasia is considered pure evil will inevitably add traces of negative affect to that concept. And if you have been raised in a family culture that placed a strict ban on the use of swear words (e.g., you would be forced to wash your mouth with soap whenever you used one), this is bound to add some traces of affect to your representation of the consequences of their use (see Jay, 2009). The same associative learning will inevitably shape the meaning of such things as emojis, intonation contours, or particular constructions (e.g., "*surely* you know that . . ."): to the extent that their usage reliably correlates with affective experiences, memory traces will simply be formed (see earlier discussion in this chapter; and see van Berkum, 2018, for a more detailed ALC analysis of word valence). Crucially, when the sign at hand is encountered again, these affective memory traces will be retrieved early in processing (see Citron, 2012, for neurolinguistics evidence).

Interpreting the Speaker's Communicative Move

The goal of language comprehension, however, is not to retrieve the stable meaning of words (and other signs) and combine those meanings into a "sentence meaning" in a way that respects the rules of grammar. The goal is to work out the contextualized "speaker meaning": What does X mean, *intend*, by presenting this composite sign to Y *here and now*? As indicated in Figure 29.1, these processes can take their cue from language, but also, and in principle no less powerfully, from other types of signs, such as a pointing gesture, a particular glance, or an emoji. And, as forcefully argued by pragmatics researchers (Clark, 1996; Levinson, 2006; Scott-Phillips, 2015; Sperber & Wilson, 1995; Tomasello, 2008), the processes involved do not just tie up a few loose ends after syntactic and semantic processes have done all of the serious work—they are a crucial part of why our species has such powers of communication. In the subsequent sections, I discuss the main types of inferential processes involved, primarily based on Tomasello's (2008) analysis.

Inferring the Speaker's Referential Intention. One important ingredient of interpreting a communicative move is to *infer the speaker's referential intention*, i.e. to work out what concrete situation the speaker is talking about exactly, and to build a *situation model* that adequately reflects this (Johnson-Laird, 1983; Zwaan, 1999). With "Even *John* thinks euthanasia is acceptable in this case," for example, the addressee needs to work out who is referred to by "John," what is being asserted about this person, and, as part of that, what "this case" refers to. Because situation models are always complex multi-component structures, there may be multiple ECSs triggering an affective response. In the case at hand, for example, the entire situation described (i.e., the fact that even John thinks that such-and-such is OK) can be an ECS for the addressee, but the referent of "John" can also itself trigger emotions (e.g., when the addressee is not on good terms with this person), and the composite "euthanasia is acceptable" (a statement that might itself clash with moral values of the addressee) can do so, too. With "We've run out of dog food," the situation model computed by the addressee will depict, in some way, a situation in which the household at hand has no dog food in stock, and, based on plausible pragmatic inferences, in which the dog(s) living there might thus get very hungry—owners who love their dogs will usually not be indifferent to that situation. Even the situation delineated by "The number 7 is *also* a prime number" can be exciting, or boring, depending on one's inclinations. The possibilities are infinite: whatever we can talk about, reality or fiction, verbally or nonverbally, might and *will* often be stuff we care about, too.

Inferring the Speaker's Stance. A second ingredient of interpreting a communicative move is to *infer or detect the speaker's stance*, his or her orientation to a particular state of affairs or "stance object" under discussion (Du Bois, 2007; Kiesling, 2011; Kockelman, 2004). Stance has an epistemic and an affective side. Epistemic stance is about aspects of the speaker's knowledge state, such as when speaker X expresses, "The number 7 is *also* a prime number" in a way, signaled by tone of voice, facial expression, body posture, and so on, that conveys certainty and confidence, or uncertainty instead. Depending on circumstances, this can sometimes be a trigger for emotions. However, the speaker's *affective* or *evaluative* stance (Hunston & Thompson, 2000), his or her *emotional* orientation toward some stance object, will *as a rule* trigger emotion in the addressee. The reason is that we are simply immediately sensitive to such emotional displays of our conspecifics, via various evolutionarily sensible routes. These include several aspects involving empathy (Decety & Cowell, 2014)—simple emotional sharing ("resonance," "mirroring," "emotional contagion"), empathic concern ("caring for"), and affective perspective-taking (i.e., more deliberately imagining somebody else's feelings)—as well as various other rapid interpersonal interlockings of social emotions (Fischer & Manstead, 2016), such as when rage instills fear, admiration instills pride, and contempt instills shame, at least initially. Returning to our examples, if the math teacher utters, “The number 7 is *also* a prime number” with clear signs of annoyance and contempt, the addressee might feel ashamed, while signs of sympathy, patience, and encouragement will typically generate more positive emotions. The stance signals that might accompany “Even *John* thinks euthanasia is acceptable in this case”—signals that, for example, reveal deep sorrow, incredulous disbelief, rage, or contempt—will also easily trigger strong or weak emotion in the addressee. The same holds for stance signals accompanying “We’ve run out of dog food,” such as those that betray unpleasant surprise, concern, or reproach.

While stance itself is usually detected relatively easily, what the stance is *about* often requires some additional computation. Speaker X’s uncertainty or annoyance, for example, might be about what is being referred to, but also about addressee Y, about the communicative situation, or about the expected effect of the utterance. Also, the stance signals emitted by speaker X need not all have been communicated *deliberately*. Furthermore, in line with the fact that much of cognition and emotion is unconscious, addressee Y may be affected by these signals without being aware of it at all. Either way, the speaker’s stance will have an impact on the addressee, via its contribution to the inferred social intention, but, unavoidably, also *by itself*.

In the example at hand, the *verbal* ingredients of the utterance single out a situation that X wishes to draw Y’s attention to, and *nonverbal* ingredients mostly signal X’s stance. But, as indicated by crossing arrows in the center of Figure 29.1, things can be otherwise. Referents can be signaled verbally but also entirely nonverbally, by such means as eye movements, manual pointing, or an iconic gesture (Tomasello, 2008). Also, epistemic or affective stance can be expressed through such nonverbal signs as tone of voice, but also by one’s choice of words and constructions, in a wide range of subtle and less subtle ways (e.g., using “I guess that . . .” to express uncertainty, “just” to express non-commitment, or swear words to express strong negative stance). The division of labor between how verbal and nonverbal parts of the composite sign signal referents and stance can change with every utterance. In fact—and important to keep in mind—the comprehension process depicted in Figure 29.1 can also work without language (Levinson, 2006; Tomasello, 2008), as when we communicate something with a well-timed silence, a raised eyebrow, an emoji, or a sigh.

Inferring the Speaker’s Social Intention. Addressee Y’s mental representations of speaker X’s referential intention and (deliberately or accidentally conveyed) stance jointly provide the basis for the third ingredient of interpreting a communicative move, the *inferring of X’s social intention*. What is it that speaker X presumably wants to achieve by making this specific move, here and now? The options are unlimited. However, according to Tomasello (2008), speakers have three major types of social motivations for communicating, often mixed in the same move, but conceptually distinct: (1) *requesting (or manipulating)*: I want you to do or know or feel something that will help *me*; (2) *informing*: I want you to know something because I think it will help or interest *you*; and (3) *sharing*: I want you to feel something so that we can share feelings together. Obvious verbal examples are “Please close the door”; “Hey, you dropped your wallet”;

and “Isn’t that a great view!” In the right context, similar intentions can be expressed by pointing to a specific open door, wallet, or view in a certain manner. Whatever the case might be, addressee Y needs to figure out what speaker X wants him or her to do, know, or feel.

The representations that we construct for an interlocutor’s social intention on the basis of his or her referential intention and stance, as well as our own expectations, are usually emotionally competent, and sometimes very strongly so—after all, it is at *this* level that we deal with each other. In the prime number example, addressee Y might infer that X just wants to help, wants to make the addressee feel small, or wants to share amazement with him or her about this mathematical fact. In the dog food example, Y might infer that X wants him or her to go to the store and wishes to phrase this as a polite request, and/or that X wants him or her to feel remorse for not having done so before. And with “Even *John* thinks euthanasia is acceptable in this case,” the social intention might be to persuade the addressee to agree to euthanasia, to mock the addressee for an obviously backward opinion, or to simply share amazement over the ease with which people apparently consider euthanasia. Note that the same utterance can realize very different social intentions, and that addressees can (and, unfortunately, fairly often do) infer different intentions from the one the speaker had in mind. In any case, many of the strong or subtle emotions elicited by language use will arise at this level of interpersonal interaction, the level where we manipulate, help, or share feelings with each other.

Communication always involves an additional “special” social project: not only has the speaker decided to use language and/or nonverbal signs to realize his or her primary social intention(s), but he or she must somehow get the other person to (implicitly or explicitly) agree to and *collaborate on the joint communicative project* for a certain amount of time. The implication is that whenever speaker X is drawing Y’s attention to his or her wish to communicate (e.g., by presenting words and other obviously communicative signs, possibly accompanied by special *for-you* signals such as eye gaze), addressee Y already knows at least *one* social intention, namely that speaker X is trying to realize whatever other social intention he or she might have via a communicative project. Importantly, the addressee may feel good about this, or not. If you are engaged in mental arithmetic and afraid to lose track, you may not want to be disturbed by communicated math trivia right now. If you are busy pondering your own view on euthanasia, you may not want somebody to tell you about other people’s opinions. And if you are fed up with working on an exam or a paper, *any* remark from anybody might be a welcome distraction, even if it is about household supplies being low.

Inferring Bonus Meaning. Working out speaker X’s referential intention, stance, and social intention (and recognizing his or her communicative intention as a special case of the latter) completes the process of inferring or understanding *speaker meaning*, that which the speaker aims to convey or bring about. Some would argue that language processing stops there (e.g., Clark, 1996). But regardless of such discipline-based demarcation lines, *processing* doesn’t of course stop there—addressee Y will consciously or unconsciously always infer (via associative memory retrieval or more sophisticated computation) at least some additional "bonus" meaning, things that X did not mean to convey at all, about speaker X (e.g., "X is a really kind teacher"; "X is getting rather forgetful"; "X is always bringing John up"), the relationship between X and Y (e.g., "X really thinks I can do better"; "X is always nudging me"; "X never listens to me") and the rest of life (e.g., "I may really have a talent for math"; "Dogs are a lot of work"; "How can people be so insensitive?"). Although not part of speaker meaning proper, such bonus meaning will usually strongly contribute to whatever Y will think, feel, do, or say next.

The Addressee's Current Emotional State Can Affect Processing

Finally, the addressee's current emotional state can also affect processing, in part fully independently from the speaker's communicative move and the active representations that reflect its analysis. First, a preceding event may have led to a strong emotion with attentional and other cognitive effects that impact further processing; such short-lived emotional state changes occur rapidly enough such that the beginning of an utterance can affect the processing of its continuation. Second, mood can impact cognitive processing in ways that are independent of whatever information happens to flow through the processing system. This also holds for *language* processing, where mood has been shown to affect, among other things, syntactic parsing (e.g., Vissers, Virgillito, Fitzgerald, Speckens, Tendolkar, Van Oostrom, & Chwilla, 2010), referential anticipation (e.g., van Berkum et al., 2013) and the response to unexpected concepts in discourse (e.g., Federmeier, Kirson, Moreno, & Kutas, 2001). Furthermore, the current emotional state can interact with the valence of information flowing through the system (cf. mood incongruency effects; e.g., Egidi & Caramazza, 2014; Pratt & Kelly, 2008). The ALC model allows one to think about the impact of mood and shorter-lived emotional states in a more precise way, by localizing that impact in one or several specific component processes.

Additional Complexity

The structured nature of representations generated by linguistic communication allows for more complexity than discussed so far. First, because active representations of a given type can be nested in representations of the same type, ECSs can also be embedded in other ECSs. Such embedding was already exemplified at the situation model level ("Even *John* thinks euthanasia is acceptable in this case"), but interesting variants also occur at the level of social intentions. Consider "You are really ugly!" spoken by a friend in a benign teasing way. The social intention ultimately construed by the addressee should be one of playful teasing. However, the teasing part is achieved via a *pretended* insult (i.e., another social move). This embedding reveals the recursive creativity of human interaction: just like in art, people can always take an established communicative pattern and start "playing" with it. However, this also opens up the possibility that although the "outermost" social move is a positive ECS, the embedded social move can still serve as a negative ECS.

A second level of complexity arises in narrative, the stories people tell each other, such as when they gossip, write a novel, or report on events in the news. Such stories are usually about other people, *characters*, engaging with each other in a series of more or less fortunate events. Not only are these characters themselves affective creatures, caring about those events in ways that make sense from their own value systems, but we as readers or listeners affectively orient ourselves toward all that as well—this is precisely the fun of reading a novel, or gossiping about others. From a modeling perspective, things get very complex here. To the degree that we get transported into the story world (e.g., Slater, Johnson, Cohen, Comello, & Ewoldsen, 2014) and identify with particular characters, for example, we may momentarily take on somebody else's value system (i.e., not just see the world through their eyes, but *feel it through their emotions*). The result of this may well be something akin to bi-stable perception, with stimuli that can be, say, a positive ECS for the character you momentarily identify with in the story world, but a negative ECS for you in the real world (see also the following section). Furthermore, in narrative, the really exciting events are often *communicative* moves, requiring you to unpack the referential intention, stance, and social intention of the communicating character, just as you would with a real interlocutor. And then on top of all that, somebody—an author, a narrator—is *telling* you this story, with an affective stance of his or her own.

This is not the place to unpack this additional complexity, nor to suggest that with the current ALC model in hand, things will always remain tractable. At the same time, it should be obvious that with a less articulate model—one that does not at least separate signs from the speaker's referential intentions, stance, and social intentions plus some bonus, or one that merely characterizes the comprehender as a TCP/IP-decoding computer—we do not stand a chance at all.

Using the ALC Model to Interpret Neurolinguistics Research Findings

By combining established ideas from the psycholinguistics of word and sentence processing, the pragmatics of interpretation, and the nature of emotion, the ALC model makes explicit that emotion can in principle pervade *every* step of the language-comprehension process, and that mood and other aspects of one's affective state can in principle impact on *all* components of the comprehension process. Of course, this does not mean that every potential interface between emotion and language is always highly relevant to every bit of actual language use. What the model is supposed to do is list the options, and help researchers think about what the operative interfaces might be in the situations they wish to study, or have already studied. To illustrate this, I will briefly examine the results of a few neurolinguistics studies that I was involved in.

EEG Research on the Processing of Insults with Swear Words

In a recent EEG study, Struiksma, De Mulder, and Van Berkum (2018) examined the short-term impact of verbal insults. Participants read verbal insults that contained relatively coarse swear words (e.g., "<X> is a bitch"), insults without such swear words (e.g., "<X> is a liar"), and compliments (e.g., "<X> is a darling"), where <X> would be replaced by the participant's own name or that of somebody else. To examine the robustness of any differential insult effects, insults were repeated in homogeneous blocks (e.g., 30 insults targeting you) that occurred three times over the course of the experiment. Relative to compliments, insults with coarse swear words elicited an early P2 effect at 150–250 ms after presentation of the critical word, regardless of who was targeted by the insult. On the assumption that being referred to in a strongly negative way is more evocative for the person him- or herself than for somebody else, the insensitivity of this effect to who was being insulted suggests that the ECS at the root of the P2 effect is *not* the specific situation referred to, nor the (imaginary) speaker's social intention. What is more likely is that the swear word elicits this response at the level of the atomic sign (see van Berkum, 2018, for a swear-word-oriented ALC analysis of word valence), and/or at the level of the inferred stance of the speaker. The early timing of the ERP effect, and the fact that it does not diminish with rather massive repetition, speaks in favor of a sign-level ECS.

In the same study, insults with coarse swear words also elicited an LPP (late positive potential) effect around 350–500 ms, again regardless of who the target was. As with the P2 effect, such independence would not be expected if the ECS emerges at the level of the inferred referential or social intention. The ALC model suggests several other options. One is that the LPP effect reflects some downstream consequence of the *same* sign-level swear-word-conditioned ECS that also elicited the P2 effect, such as, for example, increased conscious processing of salient signs. Another option is that the LPP effect is independently triggered by the inferred stance of the speaker, or by some bonus inference associated with that. The Struiksma et al. (2018) data do not allow us to decide the issue. What should be clear, though, is that the ALC model can help in delineating what the various sources of the response to verbal insults might be.

fMRI Research on the Processing of Face-Saving Indirect Replies

Bašnáková, Van Berkum, Weber, and Hagoort (2015) used fMRI to investigate the neural correlate of comprehending face-saving indirect replies. In a scripted job interview situation, participants queried several candidates over the intercom, and, at critical moments, received either a direct reply (e.g., "I am planning to take a language course this summer" to the question "What are your plans after graduation?") or an indirect *face-saving* reply (e.g., "I am planning to take a language course this summer" to the question "Are you fluent in any foreign languages?"). In a different fMRI session, the same participants also overheard somebody else do the interview with the candidates. In both situations (i.e., as addressee or overhearer), the fMRI participants needed to fully process the answers to come to a candidate-selection decision.

Relative to direct replies, indirect face-saving replies engaged core nodes of the metalizing network (bilateral temporoparietal junction (TPJ), medial prefrontal cortex, and the precuneus), as well as structures associated with other non-emotional aspects of discourse complexity (bilateral BA45, BA47, anterior temporal lobe), and did so equally when fMRI participants were the addressees of these replies and when they were merely overhearers. This is compatible with the ALC model, in that cognitive perspective-taking, as well as other aspects of discourse-level comprehension, is a necessary part of inferring the speaker's referential and social intention *regardless* of whether the listener is being addressed or overhearing. However, whether participants were the addressees of the face-saving replies or merely overhearing them did matter to whether indirectness additionally engaged *emotion-related* areas: face-saving indirectness increased activation in the left and right insula and the ACC *only* when fMRI participants were addressed themselves, not when they overheard the replies being given to somebody else. Note that in this study, face-saving replies are such that they "cover up" potential shortcomings of the job candidate, and can thus be seen to mislead or otherwise "socially navigate" the addressee. This may well explain why those addressed are uniquely, and *affectively*, sensitive to such replies. The ALC model provides two clear options as to where the addressee-specific ECS(s) might be located. One is the inferred social intention, which might involve emotionally evocative things like "he's deliberately avoiding a straight answer to cover up his shortcomings" or "he's playing me," and may as such elicit irritation or other relatively arousing emotions. The other plausible location for one or more ECSs is the associated bonus meaning (e.g., stereotypical ideas about the type of person who would do such a thing). As presented in Bašnáková et al. (2015) in detail, the ALC model allows us to systematically think about which cognitive processes are taxed equally by indirectness, as well as which of the resulting representations might specifically be emotionally evocative for addressees.

Facial EMG Research on the Processing of Morally Loaded Stories

In two recent studies, 't Hart et al. (2018a, 2018b) explored the processing of utterances such as "Mark was furious when . . ." or "Mark was happy when . . . ," embedded in a narrative fiction context where the protagonist had just exhibited morally sound or morally bad behavior. Electromyographic recordings of corrugator supercilli ("frowning muscle") activity suggested that the emotional response of readers in these experiments involved a blend of two processes: *simulating* what was being asserted, and *evaluating* what was being asserted. Evidence for the latter came from the observation that while readers frowned more when reading "Mark was furious" as compared to "Mark was happy" if the protagonist at hand had just been portrayed as a morally good person, they frowned *equally* to "Mark was furious" and "Mark was happy" if the protagonist at hand had just been portrayed as a morally *bad* person. This suggests that, as might be expected (Greene, 2014), readers have different emotions about something bad happening to bad people (e.g., *Schadenfreude*) as compared to something bad happening to good people (e.g., compassion). However, reading about furious versus happy protagonists also made an independent *additional* contribution to the recorded degree of frowning, indicating that our readers also had emotions as part of embodied language processing, in line with earlier work on this topic (e.g., Foroni & Semin, 2009; Havas, Glenberg, Gutowski, Lucarelli, & Davidson, 2010).

The ALC model allows us to more precisely delineate these various sources of reader emotion. As for simulation, the increased frowning recorded when people read sentences such as "Mark is furious" can reflect the retrieval of the meaning of the lexical signs (in this case, of "furious"), and/or the construction of a situation model (i.e., imagining a furious specific protagonist). As for evaluation, the most likely source of emotion here is how the entire situation referred to relates to the reader's own norms and values. In the fictional narratives at hand, the author's stance or social intention is not very likely to be an ECS. However, it is easy to imagine narratives where the author's or speaker's stance and social intention do matter (e.g., blogs, gossip) and will thus have the potential to trigger additional emotion. In all, the ALC model helps in making explicit where the various weak and strong emotions that we have when we are reading or listening to stories may actually come from: all the usual options discussed earlier, *plus* the embodied situation-model simulation of *somebody else's* real or fictional emotions.

EEG Research on How Mood Affects Language Processing

Language processing research with so-called implicit causality verbs has shown that when people read "David praised Linda because . . . ," the verb and the surrounding construction lead them to anticipate more information about Linda, not David; if a subsequent pronoun is inconsistent with that expectation, as in "David praised Linda because he . . . ," readers slow down and also display immediate processing costs that show up in the EEG, right at the critical pronoun (see van Berkum, Koornneef, Otten, & Nieuwland, 2007, for data and review). Of relevance here, a follow-up EEG study (van Berkum et al., 2013) indicated that the anticipatory bias varies with the participant's current mood: while readers in a good mood do show EEG traces of verb-based anticipation at an expectation-disconfirming subsequent pronoun, readers in a bad mood no longer seem to anticipate who's going to be talked about next. In terms of the ALC model, at "David praised Linda because . . . ," a bad mood seems to down-regulate the rapid, real-time anticipation of the author's referential intention, plus possibly of the plausible signs associated with that anticipated referential intention (in this case, the word "she"). More generally, Figure 29.1 can be said to make the hypothesis space for mood effects on language processing explicit, with mood potentially affecting all processes depicted on the left, and potentially biasing processing toward particular representations on the right. In the experiment at hand, mood had an impact on the degree to which readers anticipated aspects of the referential intention. At the same time, the absence of a mood-modulated ERP effect to syntactic number agreement violations (van Berkum et al., 2013) indicated that, in this study, the comprehender's affective state did not affect aspects of syntactic processing.

IMPLICATIONS

So, is human emotion just a topic, a cause, or a consequent of particular instances of language use, cleanly separated from the machinery that does the language processing, and thus of little relevance to psycholinguistics? The central claim of the ALC model is: usually not. *Every* representation retrieved or computed as part of language comprehension can in principle be an emotionally competent stimulus, with access to the brain's affective systems via fresh appraisal or associative memory traces of past appraisal and emotion; that is, *for every communicative move*, the individual signs used by the speaker can be ECSs, the situation the speaker is believed to refer to may contain one or more ECSs, the speaker's stance is usually an ECS, the inferred speaker's social intention is usually an ECS (and there may be several such intentions packed in the same move), the communicative project may itself also be an ECS, and some part of the bonus meaning will often contain one or several ECSs. In addition, the resulting or prior background emotional state can tune and bias elements of subsequent language processing, in ways that reflect how mood, emotions, and evaluations tune other forms of cognition and action. In all, emotion does not just come into play after some "thermo-insulated" cold comprehension module has done its thing. The process of language comprehension is infused with emotion right from the start, and all the way through.

Although the examples discussed have often foregrounded spoken conversation, the ALC model is also about *written* language comprehension, such as when reading a text message on your phone, a blog on the web, a textbook in class, a tax letter on your doorstep, or a novel in bed. Also, with its equal foregrounding of verbal and nonverbal signs, the ALC model can easily be applied to multi-modal instances of communication, such as when words and emojis are mixed together during texting. In fact, we can take *all* of language out and use the ALC model to analyze the impact of completely nonverbal communicative moves, such as an isolated emoji in WhatsApp, a raised eyebrow in face-to-face conversation, or a communicatively intended touch. The ALC model is really about the processing of communicative moves, whatever their form.

Who Is the Model for?

Apart from helping to make sense of past neurolinguistics research, the ALC model makes several interesting predictions that can be tested with neurolinguistics methods. First, signs that have been reliably coupled with particular affectively loaded representations (e.g., of the speaker's stance or intentions, or of the typical perlocutionary effects the sign has on others) should inject their affective payload extremely rapidly in the processing stream, a prediction that can be tested with EEG and/or MEG (for relevant evidence, see, e.g., Citron, 2012; Schacht et al., 2012; Struiksma et al., 2018; see also, in this volume, Leckey & Federmeier, Chapter 3, and Salmelin, Kujala, & Liljeström, Chapter 6). Furthermore, the ALC model predicts that at least five different levels of representation computed as part of language comprehension—signs, referential intention, stance, social intention, and bonus meaning—should each have some way of access to these emotion-relevant neural structures, a prediction that can be tested with functional and structural connectivity analysis. And peripheral measures such as skin conductance and facial electromyography (EMG) can help test the model's prediction that the different levels of representation disentangled by the model can all contribute to a reader's or listener's affective response, and that the acquired affective meaning of a linguistic sign can be related to each of the various potential sources of affect higher up in the model, as language is being used in particular contexts again and again.

Several other research communities might also profit from the ALC model. For linguists, psycholinguists, and communication researchers who are asking questions about language and emotion, the model can serve as a tool for thinking about existing findings and new research, and, inevitably, as a stepping stone toward a more adequate model. Furthermore, for those in different fields that use linguistic materials ("vignettes"), the ALC model can serve as a reminder of the complexity and multileveled nature of the stimulus comprehension processes involved. The idea that words can affect people in several ways that go beyond the obvious (what they refer to) is relevant not only to researchers in basic psychological and cognitive neuroscience research on emotion, morality, and social interaction, but also to researchers who explore institutional and interactional processes in the political, judicial, educational, medical, financial, or business domains.

Finally, as an explicit model of language processing that also minds emotion, the ALC model can perhaps do other work as well. The biases discussed earlier in the chapter have led to an approach to language processing that has been fruitful: we now know a lot more than before about how the brain cracks the language code. At the same time, the biases have drawn attention away from what we *do* with language because we care about "stuff." I frequently come across professionals who have a general interest in language because of the social, verbal nature of their profession (e.g., coaching, teaching, advertisement, politics), but who feel that the language sciences currently have little to offer. Models like the once proposed here can perhaps help bridge the gap.

What if I Just Do Not Care?

What about the many researchers in language and communication who are not interested in emotion in their work? Can they just ignore the current analysis, or similar cases made by others (e.g., Besnier, 1990; Foolen, 2012; Jensen, 2014; Majid, 2012)? I would argue that even language scientists whose work is well removed from the interfaces with emotion should have some basic knowledge of what and where those interfaces are. One reason is that emotion is a powerful source of variance in language processing—a source one should be aware of and if possible control for, much like experimentalists routinely control for word frequency. More fundamentally, every language and communication researcher should know about the interfaces with emotion for the same reason for which those who work on, say, syntactic parsing should know a bit about phonology, semantics, and pragmatics, and why those working on text comprehension should know a bit about word recognition. We are looking at a structured yet integrated system, a bit of nature that, although it has joints to carve it at, and subcomponents to focus on, is not a collection of disconnected bits that can all be studied in isolation. If anywhere, that case can be made quite easily for emotion. People use language to refer to things they care about, and they use it to relate to each other, in ways that are almost never neutral. In the words of Nico Besnier (1990, p. 433):

> Affect permeates all utterances across all contexts because the voices of social beings, and hence their affect, can never be extinguished from the discourse.

If you combine Besnier's fundamental observation with basic cognitive neuroscience knowledge about the role of emotion in cognition and action, and about emotional learning in the brain, it is actually quite difficult to see how the study of language *processing* can be complete if emotion is not included in the picture as well.

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PART V

GRAMMAR AND COGNITION

CHAPTER 30

GRAMMATICAL CATEGORIES

DAVID KEMMERER

INTRODUCTION

GRAMMATICAL categories—also known as syntactic categories, lexical categories, word classes, and parts of speech—are fundamental to human languages because they strongly influence the ways in which conceptual structures are packaged in lexical items and, even more important, the ways in which lexical items are combined to form complex expressions. Across the roughly 7,000 languages of the world, the most basic and widely attested categories are nouns, verbs, adjectives, and adverbs. They typically make up large open classes whose memberships constantly fluctuate as new items are added and old ones fade away. In contrast, other categories tend to be both small and closed, with memberships that do not change very quickly over time. Some familiar examples from English are prepositions, conjunctions, and articles, and some lesser known examples from other languages are postpositions, classifiers, and focus markers. Although a great deal has been learned about the nature of grammatical categories during the past few decades, several competing accounts have been proposed by generative, cognitive, functional, and typological theorists, and many issues remain controversial (for a survey of approaches, see Rauh, 2010; see also Haspelmath, 2012, and the debate between Haspelmath, 2007, and Newmeyer, 2007).

Recent neurolinguistic research on grammatical categories has addressed a variety of phenomena, but the vast majority of studies have been devoted to a single topic of central importance, namely the noun-verb distinction. In fact, the neural underpinnings of this distinction have been explored in countless investigations employing all of the major brain mapping methods, including deficit-lesion correlations in brain-damaged patients (see Wilson, Chapter 2 in this volume), positron emission tomography (PET), functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume), transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume), extracranial and intracranial electrophysiology (see Duffau, Chapter 8 in this volume, and magnetoencephalography (MEG; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume) (for reviews and meta-analyses see Berlingeri et al., 2008; Black & Chiat, 2003; Cappa & Perani, 2003; Crepaldi, Berlingeri, Paulesu, & Luzzatti, 2011, 2013; Druks, 2002; Kemmerer, 2014; Luzzatti, Aggujaro, & Crepaldi, 2006; Mätzig, Druks, Masterson, & Vigliocco, 2009; Pillon & d'Honincthun, 2010; Shapiro & Caramazza, 2003b, 2004; Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). As a consequence, the literature on this topic is now quite large and complex. But even though it contains a wealth of empirically solid, theoretically interesting, and clinically relevant material, there are still many unanswered questions. With the aim of providing a concise overview of the field, this chapter concentrates on some of the most prominent neurolinguistic issues regarding the noun-verb distinction. A few other topics, however, are also briefly discussed toward the end of the chapter.

Nouns and Verbs

Starting with the Universal Semantic Prototypes

According to several linguistic frameworks, the most basic grammatical categories can be characterized partly in terms of universal prototypes that are grounded in meaning (Anderson, 1997; Croft, 1991, 2000, 2007; Langacker, 1987; O'Grady, 1997; Wierzbicka, 2000). For example, Croft (1991, 2000, 2007) argues that prototypical nouns and verbs reflect certain default combinations of pragmatic function and semantic class, with nouns involving reference to objects and verbs involving predication of actions (for present purposes, "reference" is what the speaker is talking about, and "predication" is what the speaker asserts about the referent(s) in a particular utterance). Support for this proposal comes from corpus analyses that have consistently yielded the following results across diverse languages worldwide: referential constructions contain predominantly object words, and object words appear predominantly in referential constructions; similarly, predicative constructions contain predominantly action words, and action words appear predominantly in predicative constructions.

In light of these considerations, it is not surprising that the lion's share of neurolinguistic research on basic grammatical categories has focused on object nouns and action verbs. Some of the most influential studies have shown that each of these prototypical categories can be either selectively or disproportionately impaired by brain damage. Although relative verb deficits are more common than relative noun deficits, numerous double dissociations have been documented, especially using oral picture-naming tasks, and often the accuracy differences between the two word classes are quite substantial (see Mätzig et al., 2009, for a review of 240 previously reported patients and 9 new ones). For example, Table 30.1 presents data from 20 representative cases—10 with worse oral production of nouns than verbs, and 10 with the opposite performance profile—all of whom displayed an accuracy difference of at least 30%.

Table 30.1 Examples of Large (30%+) Dissociations Between Prototypical Nouns and Verbs in Oral Picture-Naming Tasks.

Patients with Worse Noun Than Verb Production			Patients with Worse Verb Than Noun Production		
Case	Nouns	Verbs	Case	Nouns	Verbs
Mario	7	88	BW	98	60
H.Y.	35	85	FDP	96	50
H.F.	49	83	LK	93	63
E.A.	42	82	LR	92	40
Z.B.L.	41	78	EM	90	59
S.K.	47	77	TB	88	37
M.L.	38	75	UB	87	48
S.F.	27	73	FC	87	30
E.B.A.	12	72	RE	83	35
R.G.	29	64	MB	83	35

Cells indicate percent correct.

Data from Mätzig et al. (2009).

For some patients with category-related deficits like these, the locus of the cognitive impairment appears to be at the level of conceptual knowledge, as indicated by the following forms of convergent evidence. First, the majority of errors are either omissions (i.e., "don't know" responses) or semantic substitutions (e.g., calling a penguin a duck). Second, the relevant word class is disrupted not only during production tasks like picture naming, but also during comprehension tasks like word-picture matching. Third, the lesions affect brain regions that are likely to be involved in representing the relevant kinds of concepts. This last point is elaborated in the following.

Patients who exhibit significantly greater noun than verb deficits usually have damage in the left temporal lobe, due to either a stroke (Mätzig et al., 2009) or a degenerative disorder such as Alzheimer's disease (Cappa et al., 1998) or herpes simplex encephalitis (Damasio & Tranel, 1993). These findings fit well with other literature regarding the neural substrates of the kinds of object concepts that tend to be encoded by prototypical nouns. When people process such concepts, they often retrieve various types of modality-specific object properties, including shape, color, sound, smell, taste, and manipulability (Binder & Desai, 2011). Among all of these features, however, the one that carries the most semantic weight is shape (Gainotti, Spinelli, Scaricamazza, & Marra, 2013). It is well established that the posterior and middle portions of the ventral temporal cortex are essential for recognizing objects based on perceived shape (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Kriegeskorte et al., 2008). Additionally, a great deal of data suggests that some ventral temporal regions—partly overlapping, but mostly lying next to those involved in perception—also represent shape information when words for objects are processed (Capitani et al., 2009; Martin, 2007). Moreover, compared to the comprehension of action words, the comprehension of object words engages the ventral temporal cortex quite rapidly, within about 200 milliseconds (ms) (Chan et al., 2011; Pulvermüller, Lutzenberger, & Preissl, 1999). Taken together, these discoveries support the hypothesis that the ventral temporal cortex implements the most important representational component, namely shape, of the meanings of prototypical nouns.

As for patients who exhibit significantly greater verb than noun deficits, their lesions are rather disparate, but usually one or more of the following left hemisphere areas is affected: the inferior frontal gyrus (IFG), often together with nearby motor areas; the inferior parietal lobule, especially the supramarginal gyrus (SMG); and the posterior middle temporal gyrus (pMTG). These findings come from studies of patients who have suffered either a stroke (Kemmerer, Rudrauf, Manzel, & Tranel, 2012) or a degenerative disorder such as motor neuron disease (Bak & Hodges, 2004), progressive nonfluent aphasia (Hillis et al., 2006), or corticobasal degeneration (Silveri & Ciccarelli, 2007). Such deficit-lesion correlations dovetail with other data suggesting that the implicated regions underlie the kinds of action concepts that tend to be encoded by prototypical verbs. Although the precise ways in which these regions contribute to action concepts are only beginning to be elucidated, some of the leading ideas are as follows. In the frontal lobe, the IFG—in particular, Brodmann area 44—may subserve the sequential and hierarchical organization of action concepts (Clerget, Winderickx, Fadiga, & Olivier, 2009; Fazio et al., 2010), and precentral motor areas may subserve the body-part-specific motor features of action concepts (Kemmerer, 2015a; Pulvermüller, 2013). In the parietal lobe, the SMG may subserve the spatial-relational and kinematic aspects of action concepts (Goldenberg, 2009; Kalénine, Buxbaum, & Coslett, 2010). Moreover, in the temporal lobe, the pMTG may subserve the visual motion patterns as well as the participant roles (e.g., chaser vs. chasee) specified by action concepts (Watson, Cardillo, Ianni, & Chatterjee, 2013; Wu, Waller, & Chatterjee, 2007). It is noteworthy that all of these brain regions either overlap with or lie next to regions that are recruited during the execution and observation of actions (Molenberghs, Cunnington, & Mattingley, 2012). Furthermore, compared to the comprehension of object words, the comprehension of action words engages motor-related frontal regions very quickly, within about 200 ms (Pulvermüller, Lutzenberger, & Preissl, 1999; Shtyrov, Butorina, Nikolaeva, & Stroganova, 2014). Overall, these findings support the hypothesis that the frontal, parietal, and temporal regions described in the preceding implement the core representational parameters of the meanings of prototypical verbs.

Category-Related Disorders Involving the Representation/Retrieval of Lexical Forms

So far we have focused on semantic accounts of the sorts of noun-verb dissociations that are frequently displayed by brain-damaged patients when they perform picture-naming tasks. It is important to realize, however, that such dissociations can also arise from post-semantic impairments. This is revealed in a particularly striking way by patients who exhibit word-production deficits that selectively or disproportionately affect not just one grammatical category—either nouns or verbs—but also just one output channel—either speaking or writing (Caramazza & Hillis, 1991; Hillis, Tuffiash, & Caramazza, 2002; Hillis, Wityk, Barker, & Caramazza, 2003; Rapp & Caramazza, 1998; see also Rapp & Goldrick, 2006).

For example, as shown in Figure 30.1, case M.M.L., who suffered from progressive nonfluent aphasia, manifested steadily worsening spoken production of prototypical verbs over a 2.5-year period, while her written production of prototypical verbs, as well as her spoken and written production of prototypical nouns, remained fairly accurate (Hillis et al., 2002). M.M.L.'s poor spoken production of prototypical verbs could not be due to impaired knowledge or processing of action concepts because her written production of the very same verbs was good. Instead, her remarkably specific deficit must reflect some kind of post-semantic problem.

Cases like this raise many intriguing questions about the relationships between meaning, grammar, and the modality-specific (i.e., phonological and orthographic) lexicons (for detailed theoretical discussion, see Caramazza & Miozzo, 1998; Rapp & Caramazza, 2002). Here, however, we will restrict our attention to the issue of whether the word forms in each lexicon are segregated according to grammatical category. On the one hand, the neuropsychological dissociations exhibited by patients like M.M.L. are clearly consistent with the hypothesis that the noun-verb distinction is respected at the level of lexical forms. For example, M.M.L.'s own performance profile could be explained in terms of increasing damage to just one set of words—specifically, the verb compartment of the phonological lexicon (Figure 30.2 A). On the other hand, the available data

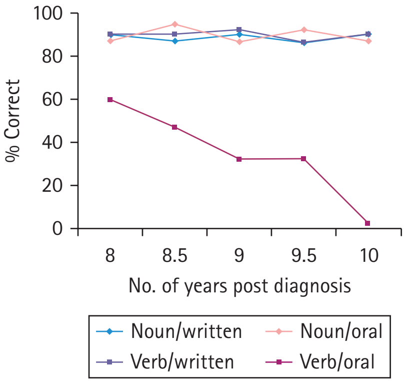

FIGURE 30.1. Longitudinal performance of the progressive nonfluent aphasic patient M.M.L. on tasks involving the spoken and written naming of objects and actions with nouns and verbs, from ~8 to 10.5 years following diagnosis. Spoken production of verbs deteriorated steadily (red plot), but written production of verbs, as well both spoken and written production of nouns, remained unaffected.

Source: Reproduced with permission from Shapiro & Caramazza (2003); original data from Hillis et al. (2002).

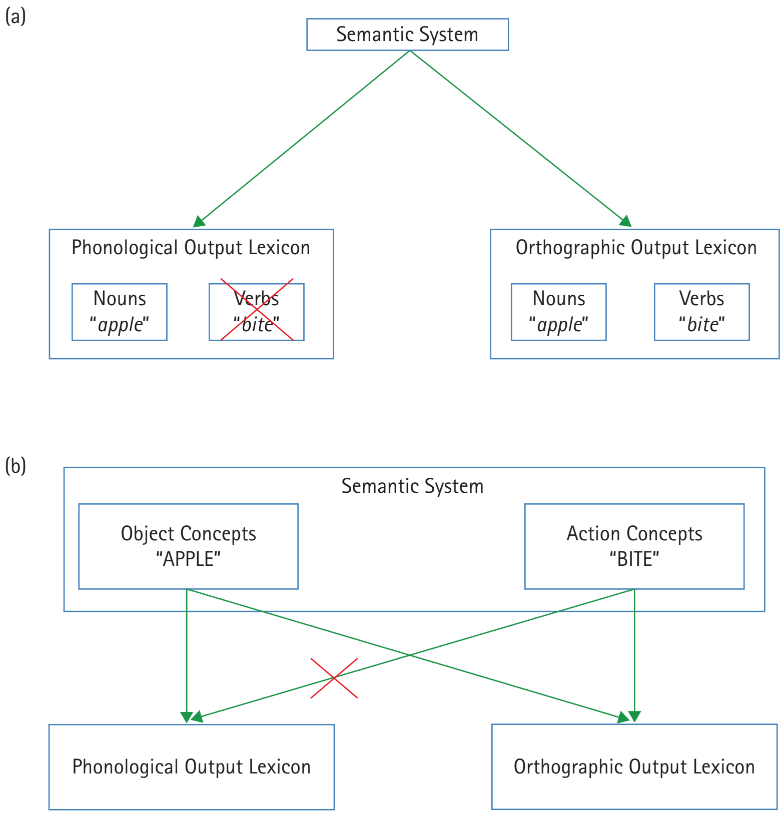
(a)
Semantic System
Phonological Output Lexicon
Nouns
"*apple*"
Verbs
"*bite*"
Orthographic Output Lexicon
Nouns
"*apple*"
Verbs
"*bite*"
(b)
Semantic System
Object Concepts
"APPLE"
Action Concepts
"BITE"
Phonological Output Lexicon
Orthographic Output Lexicon

FIGURE 30.2. Two alternative accounts of the performance profile of patient M.M.L. depicted in Figure 30.1. (A) An account that assumes segregation of nouns and verbs within the modality-specific output lexicons. (B) An account that assumes segregation of word meanings according to conceptual category within the semantic system. In each architecture, the red cross indicates the site of progressive dysfunction.

can also be accommodated by an alternative hypothesis that does not require nouns and verbs to be differentiated at the lexical level, but instead assumes that the connectional pathways between the meanings and forms of particular word classes can be independently disrupted. Applied to M.M.L., such an account could be formulated as follows: (1) the meanings of prototypical nouns and verbs are represented in separate semantic subsystems, as discussed in the previous section; (2) each semantic subsystem projects to both of the modality-specific lexicons; and (3) M.M.L.'s disorder involves increasing damage to just one route—specifically, the pathway that projects from action concepts to the corresponding verb forms in the phonological lexicon (Figure 30.2 B).

Thus, even though patients with combined grammatical category–specific and output channel–specific deficits support the view that the lexical forms of nouns and verbs are segregated in the brain, they certainly do not force such a conclusion. It is noteworthy, however, that the question of whether grammatical category distinctions are captured at the lexical level continues to be controversial, and it has been addressed from several other perspectives, as shown in the next section.

Efforts to Overcome Confounds Between Conceptual and Grammatical Factors

From a methodological point of view, there are both merits and shortcomings to deliberately designing some neurolinguistic studies so that they focus specifically on the most prototypical grammatical categories—that is, object nouns and action verbs. On the positive side, such a strategy can shed light on how the brain implements the universal prototypes identified by typologically oriented linguists like Croft (1991, 2000, 2007). On the negative side, however, conflating the conceptual distinction between objects and actions with the grammatical distinction between nouns and verbs makes it difficult, if not impossible, to discover the neural correlates of a much wider range of phenomena involving language-particular word classes. In an effort to overcome this limitation, an increasing number of researchers have begun to conduct studies in which conceptual-grammatical confounds are minimized. Two different approaches to doing this are summarized in the following. As we will see, however, both of them have generated mixed results, since some studies suggest that, *qua* lexical items, nouns and verbs are not systematically differentiated in the brain, whereas other studies suggest that they rely on at least partly separate neural networks.

Strategy 1: Closely Match the Meanings and Processing Demands of Nouns and Verbs

According to some studies, when nouns and verbs are well matched for semantic dimensions as well as processing requirements, they recruit essentially the same brain regions to the same degrees. For instance, in a PET study carried out in Italian, Vigliocco et al. (2006) asked subjects to simply listen to four sets of words. Crucially, all of the word lists were carefully created so as to allow the investigators to independently determine which patterns of brain activity were due to conceptual factors and which were due to grammatical factors:

- sensory nouns (SNs), i.e., nouns with rich sensory features (e.g., *lampi*, “lightning”)
- motor nouns (MNs), i.e., nouns with rich motor features (e.g., *giravolta*, “twirl”)
- sensory verbs (SVs), i.e., verbs with rich sensory features (e.g., *luccicano*, “shine”)
- motor verbs (MVs), i.e., verbs with rich motor features (e.g., *scuote*, “shake”).

Two contrasts were performed to identify the neural correlates of sensory words and motor words, irrespective of grammatical category, and both of these contrasts revealed activity in some of the expected areas. Specifically, with regard to sensory words, the contrast [(SNs + SVs)—(MNs + MVs)] revealed activity in the left ventral temporal cortex, and with regard to motor words, the opposite contrast [(MNs + MVs)—(SNs + SVs)] revealed activity in the left lateral motor cortex. In addition, and more important, two contrasts were performed to identify the neural correlates of nouns and verbs, irrespective of conceptual considerations; however, neither of these contrasts yielded any significant effects whatsoever, even when the investigators switched from whole-brain analyses to region-of-interest analyses. More precisely, no activity was revealed by the contrast [(SNs + MNs)—(SVs + MVs)], which was meant to identify regions unique to nouns, and likewise, no activity was revealed by the opposite contrast [(SVs + MVs)—(SNs + MNs)], which was meant to identify regions unique to verbs. What these findings suggest is that when conceptual-grammatical confounds are reduced, and when computational loads are also controlled, nouns and verbs are not segregated in the brain, but instead depend on shared neural resources (see also Barber, Kousta, Otten, & Vigliocco, 2010; Siri et al., 2008; Vigliocco et al., 2011; as well as Collina, Marangolo, & Tabossi, 2001; Pulvermüller, Mohr, & Schleichert, 1999; and Tabossi, Collina, Pizzioli, & Basso, 2010).

On the other hand, there is some recent evidence for the view that nouns and verbs do recruit at least partly separate neural networks, even when their meanings and processing demands are fairly similar. Focusing once again on Italian, Tsigka, Papadelis, Braun, and Miceli (2014) conducted an MEG study in which participants silently read noun-verb homonyms in two syntactically minimal contexts that each had two variants (for a similar study in Spanish, only using event-related potentials, see Yudes, Domínguez, Cuetos, & de Vega, 2016):

- article + noun
  - singular (e.g., *il ballo*, "the dance")
  - plural (e.g., *i balli*, "the dances")
- pronoun + verb
  - first-person singular (e.g., *io ballo*, "I dance")
  - second-person singular (e.g., *tu balli*, "you dance").

The results of source analyses using minimum norm estimates (MNE) are depicted in Figure 30.3. Looking first at the time windows for function word processing, it can be seen that the articles and pronouns activated essentially the same posterior bilateral areas; however, relative to the articles, the pronouns evoked greater activity at right parietal sites during the 88–108 ms window and at left prefrontal sites during the 232–251 ms window. Turning now to the more interesting time windows for content word processing, what stands out most clearly is that the verbs elicited more extensive and robust activity than the nouns over the entire course of measurement—initially in right parietal clusters during the 115–136 and 195–212 ms windows, then in bilateral central and midline regions during the 280–300 ms window, next in the left IFG during the 297–319 ms window, then in a large left parietal cluster during the 380–397 ms window, and finally again in the left IFG during the 393–409 ms window. Because the noun-verb homonyms were very close in meaning, the neurotopographic differences that emerged between

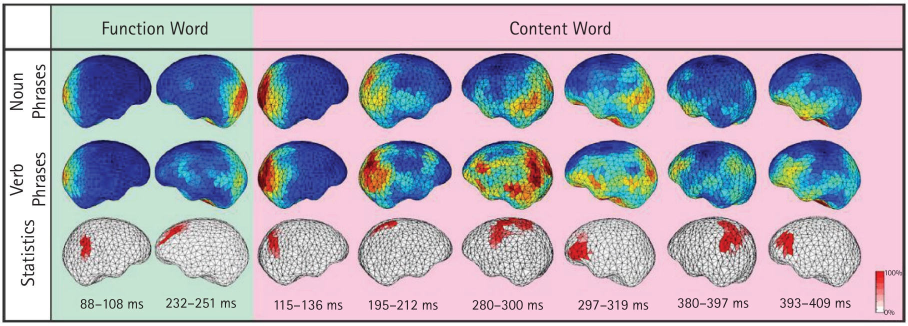

FIGURE 30.3. MEG-based minimum norm estimates (MNEs) for the time windows during which significant differences between visually presented noun-phrases (NPs) and verb-phrases (VPs) were revealed by cluster analysis. The top and middle rows display the averaged MNEs of NP-and VP-related activity across the consecutive time slices for which cluster analysis revealed significant differences between NPs and VPs. The bottom row shows the extension of clusters that significantly differed between NPs and VPs. Significant clusters were defined as spatially and temporally contiguous brain regions (>10 vertices; >12 samples) whose spatial extent, however, could vary over time. To indicate the stability of the cluster, the percentage of samples with respect to overall temporal persistence of the cluster is coded by color intensity. A value of 100% indicates that the corresponding vertex belonged to the cluster throughout the cluster's lifetime. Green and pink backgrounds indicate time windows corresponding to the presentation of function word and content word, respectively.

Source: Reproduced with permission from Tsigka et al. (2014, p. 92).

them are unlikely to reflect conceptual factors. Hence, according to Tsigka et al. (2014, p. 95), the findings "invite the conclusion that at least partly separable neural substrates are involved in processing grammatical class information and the corresponding morphosyntactic operations." However, given that the homonymous nouns and verbs engaged many of the same regions, only with verbs activating them more strongly, the authors acknowledge that the data do not completely rule out the possibility that the two categories have some cortical underpinnings in common at the lexical level.

Strategy 2: Investigate Both Concrete and Abstract Nouns and Verbs

Pursuing another approach to disentangling the conceptual and grammatical aspects of word classes, Moseley and Pulvermüller (2014) carried out an fMRI study in which participants silently read the following four types of stimuli:

- concrete nouns (e.g., *mouse*)
- concrete verbs (e.g., *chomp*)
- abstract nouns (e.g., *truce*)
- abstract verbs (e.g., *glean*)

Analyses of the imaging data revealed a significant interaction between conceptual (i.e., concrete vs. abstract) and grammatical (i.e., noun vs. verb) factors, especially in left frontocentral regions. Further exploration, however, indicated that although the concrete nouns and verbs triggered distinct patterns of cortical engagement, the abstract nouns and verbs did not. Based on these results, the authors concluded—in a manner similar to Vigliocco et al. (2006)—that when neurotopographic differences are observed between nouns and verbs in single-word processing tasks, they reflect semantic factors rather than lexical segregation.

On the other hand, an earlier study by Berndt, Haendiges, Burton, and Mitchum (2002) used neuropsychological methods to support the hypothesis that nouns and verbs have at least partly distinct neural substrates, regardless of whether their meanings are concrete or abstract. The investigators administered two kinds of tasks to seven brain-damaged patients. The first task employed a standard oral picture-naming paradigm to assess the patients' retrieval of prototypical object nouns and action verbs. The second task, however, employed an auditory sentence-completion paradigm to assess the patients' retrieval of not only concrete nouns and verbs, all of which had high imageability, but also abstract nouns and verbs, all of which had low imageability. Some examples of the four conditions are as follows:

- concrete noun (e.g., *scale*): *Bonny had been following a strict diet. To find out if it was working, she weighed herself on the _____.*
- concrete verb (e.g., *rob*): *The bandits were planning their next holdup. They needed to decide which bank would be easiest to _____.*
- abstract noun (e.g., *fault*): *Jennifer was upset that she might be blamed for the accident. She hoped everyone knew that it wasn't her _____.*
- abstract verb (e.g., *stay*): *Andy found it difficult to visit his mother in the hospital. He wanted to get away, but she wanted him to _____.*

The seven patients exhibited several different kinds of performance profiles across the tasks, but for present purposes the most interesting case was R.E. As shown in Figure 30.4, she manifested significantly worse production of verbs than nouns across the board, with no effect of imageability in the sentence-completion task (for similar data from other patients see Crepaldi et al., 2006). This demonstrates that, irrespective of conceptual considerations, verbs can be disproportionately impaired relative to nouns. And this in turn provides some leverage for the view that the neural substrates of word classes are determined to some extent by genuinely grammatical factors.

Focusing on Inflection

Another way in which researchers have transcended the limitations of prototypical nouns and verbs is by investigating category-specific morphosyntactic operations that are not constrained by the conceptual distinction between objects and actions. So far,

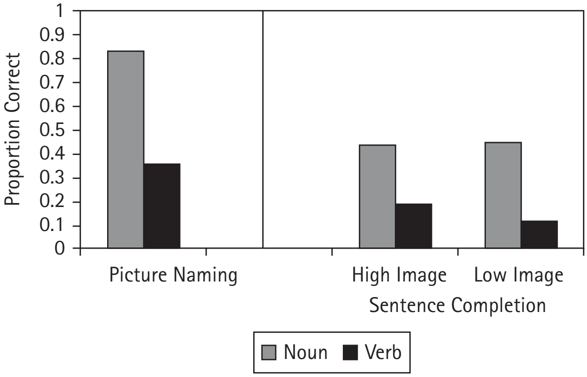

FIGURE 30.4. Proportion of correct responses by patient R.E. for nouns and verbs in a task involving object/action picture naming (left panel) and in a task requiring sentence completion with target words rated as having high or low imageability (right panel). Verb production was significantly worse than noun production in both tasks, and there was no effect of imageability in the sentence completion task.

Source: Reproduced with permission from Berndt et al. (2002, p. 361).

most of this work has attempted to elucidate the neural networks that underlie number inflection for count nouns (e.g., *I have two thoughts about that*) and tense/agreement inflection for main verbs (e.g., *Yesterday I developed a new plan*). Overall, the literature suggests that during production tasks, these two types of category-specific morphosyntactic operations depend on neural networks that are partly shared and partly segregated (for reviews, see Kemmerer, 2015b, Chapter 13; Shapiro & Caramazza, 2009). Broca's area (i.e., BAs 44 and 45 in the left IFG) seems to implement a relatively late stage of processing that occurs just before morphophonological encoding and that is essentially the same for the two classes of words (Cappelletti, Fregni, Shapiro, Pascual-Leone, & Caramazza, 2008; Sahin, Pinker, Cash, & Halgren, 2009; Sahin, Pinker, & Halgren, 2006). However, the computation of appropriate morphosyntactic features—that is, number features for count nouns and tense/agreement features for main verbs—seems to take place during an earlier, higher-order stage of processing, and at this stage the operations for the two classes of words appear to have separate neural underpinnings.

Some of the evidence for this view comes from neuropsychological studies that have revealed double dissociations between number inflection for count nouns and tense/agreement inflection for main verbs. For example, Shapiro, Shelton, and Caramazza (2000) and Shapiro and Caramazza (2003a) reported two stroke patients, J.R. and R.C., who were given two tasks that required them to complete sentence frames with the correctly inflected forms of words. In the first task, the key words were real noun-verb homonyms that had equivalent forms and closely related meanings (e.g., *a guide; to guide*). As shown in the following, two sentence frames called for singular and plural forms of count nouns, and two sentence frames called for third-person plural and third-person singular forms of main verbs:

- Inflection of real nouns
  - *These are guides; this is a _____ (guide-ø)*
  - *This is a guide; these are _____ (guides)*
- Inflection of real verbs
  - *This person guides; these people _____ (guide-ø)*
  - *These people guide; this person _____ (guides)*

In the second task, the key words were pseudo-noun-verb homonyms (e.g., *a fleeve; to fleeve*), which gave the researchers even more assurance that if the patients responded differently to the two categories, it could not be due to either phonological or conceptual factors. As shown in the following, the sentence frames were identical to those employed in the first task:

- Inflection of pseudo-nouns
  - *These are fleeves; this is a _____ (fleeve-ø)*
  - *This is a fleeve; these are _____ (fleeves)*
- Inflection of pseudo-verbs
  - *This person fleeves; these people _____ (fleeve-ø)*
  - *These people fleeve; this person _____ (fleeves)*

The central finding was that the two patients manifested opposite performance profiles for the two types of inflection, and their dissociations were present for both real words and pseudo-words. In particular, J.R. was significantly worse at inflecting count nouns for number than main verbs for tense/agreement, whereas R.C. was significantly worse at inflecting main verbs for tense/agreement than count nouns for number (for similar dissociations displayed by other patients, see Benetello et al., 2016; Laiacona & Caramazza, 2004; Tsapkini, Jarema, & Kehayia, 2002). In their discussion of the complementary deficits exhibited by J.R. and R.C., Shapiro and Caramazza (2003a, p. 1194) emphasize that in both cases the disrupted capacities are not only category-specific, but also "seem to be grammatical, and not directly involved in retrieving stored information about word form or meaning; otherwise it is not clear how we might account for the observed deficits with pseudo words, which presumably have no memorized features."

The discovery that certain morphosyntactic operations for count nouns and main verbs can be differentially impaired raises the question of which brain regions subserve those operations. Unfortunately, very little is known about the regions that underlie the computation of number features for count nouns, but there are some hints that this process may depend on cooperative interactions between the left mid/anterior fusiform gyrus, the left inferior parietal lobule, and the superior portion of Broca's area (Sahin et al., 2006; Shapiro & Caramazza, 2009; Shapiro, Moo, & Caramazza, 2006, 2012; see also Domahs et al., 2012). On the other hand, considerable progress has been made in identifying the regions that underlie the computation of tense/agreement features for main verbs, with most of the data pointing to a network involving the left posterior middle temporal gyrus (pMTG) and the left middle frontal gyrus (MFG). Here we will focus on the latter region and address the specific issue of whether its anterior or posterior sector is most critical.

Support for the importance of the *posterior* portion of the left MFG comes from case R.C., since he was disproportionately impaired for verb inflection, and his lesion, but not J.R.'s, extended into this territory. In addition, several fMRI studies suggest that, relative to noun inflection, verb inflection recruits the left posterior MFG immediately superior to BA 44. For instance, Shapiro et al. (2006) obtained results along these lines in a study that used real and pseudo-word tasks like those described in the preceding (see also Shapiro et al., 2012). When the verb conditions were contrasted against the noun conditions, one of the only activated areas was the left posterior MFG. The same region was also engaged significantly more by verb than noun inflection in an fMRI study by Willms et al. (2011), but these researchers went two steps further than Shapiro et al. (2006): first, they employed tasks that required English-Spanish bilingual speakers to inflect words in both languages; and second, they used multi-voxel pattern analysis to show that within the left posterior MFG the specific activation patterns elicited by the verb conditions, relative to the noun conditions, were virtually identical across the two languages. Finally, Kielar, Milman, Bonakdarpour, and Thompson (2011) recently found that both the overt and covert production of tense/agreement morphology for English verbs recruited the left posterior MFG, together with the caudally adjacent precentral gyrus. Overall, then, there appears to be a fair amount of neuropsychological and fMRI data implicating the posterior sector of the left MFG in verb-specific morphosyntactic processing.

On the other hand, a recent fMRI study by Finocchiaro, Basso, Giovenzana, and Caramazza (2010) generated results which suggest that the *anterior* portion of the left MFG also contributes to verb-specific morphosyntactic processing. The participants in this experiment performed tasks that required them to inflect Italian target words in ways that conformed to certain phrasal contexts. Some of the expressions involved count nouns (e.g., *uno starnuto*, "a sneeze"; *molti starnuti*, "many sneezes"), and others involved main verbs (e.g., *io taglio*, "I cut"; *tu tagli*, "you cut"). When the verb conditions were contrasted against the noun conditions, one of the only activated areas was the left anterior MFG, at the intersection of BAs 10, 46, and 47, immediately anterior to BA 45. Surprisingly, the posterior portion of the left MFG was not engaged.

Given these inconsistencies, it makes sense to ask whether other brain mapping methods have been used to address the same issues. In fact, a few TMS studies have yielded two relevant findings. First, Cappelletti et al. (2008) showed that, relative to sham stimulation, the application of repetitive TMS to the *posterior* portion of the left MFG did *not* interfere significantly with either verb or noun inflection. Second, both Cappelletti et al. (2008) and Shapiro, Pascual-Leone, Mottaghi, Gangitano, and Caramazza (2001) showed that, relative to sham stimulation, the application of repetitive TMS to the *anterior* portion of the left MFG *did* interfere significantly more with verb inflection than noun inflection (see also Finocchiaro et al., 2008). Taken together, these findings are at odds with the fMRI studies by Shapiro et al. (2006), Willms et al. (2011), and Kielar et al. (2011), and also with the neuropsychological data for patient R.C.; however, they are congruent with the fMRI study by Finocchiaro et al. (2010). Thus, there are still some uncertainties regarding the precise localization of the neural mechanisms that underlie tense/agreement inflection for main verbs, but these mechanisms most likely depend on *some* portion of the left MFG.

It should be clear from this brief review that neurolinguistic research on category-specific inflectional processes has been making significant headway. At the same time, however, it is important to realize that this line of work does not address the neural correlates of nouns and verbs in any sort of global (i.e., cross-constructional or construction-independent) sense; instead, it only addresses the neural correlates of the particular word classes that happen to occur in the inflectional constructions under investigation. This is why the classes discussed earlier are referred to rather narrowly as count nouns and main verbs. After all, other kinds of nouns, such as mass nouns, cannot easily be pluralized (e.g., compare *books* with **muds*), and other kinds of verbs, such as modal verbs, are prohibited from taking tense markers (e.g., compare *walked* with **coulded*). Furthermore, it bears mentioning that some languages, like Vietnamese, lack all inflection, and others, like Sirionó, have inflection but employ it in peculiar ways, such as by applying tense to words that encode objects and serve as syntactic arguments of main verbs (Nordlinger & Sadler, 2004). Hence, caution is always warranted when using generic terms like "noun" and "verb" to describe the lexical categories that occur in certain constructions of certain languages (Kemmerer, 2014).

Dissociations Between Subcategories

Continuing with the notion that the major parts of speech can be broken down into multiple subcategories, this last section deals with a few strands of neurolinguistic research that have begun to explore how such subcategories are implemented in the brain. Some of the most salient findings in this small but growing literature are briefly summarized in the following (see also Fieder, Nickels, Biedermann, & Best, 2014a; Fieder, Nickels, & Biedermann, 2014b).

Proper versus Common Nouns

In the domain of nominal constructions, one of the most fundamental distinctions is between proper and common nouns. These two classes of words differ both conceptually and grammatically. Proper nouns (e.g., *Barack Obama*) designate unique entities, and in accord with this function they typically do not allow either articles or adjectives (see Van Valin & LaPolla, 2007, pp. 59–60, for a brief discussion of cross-linguistic diversity and the special interpretive adjustments required by unusual expressions like *A tired*

Barack Obama returned to the White House). In contrast, common nouns (e.g., *dog*) designate entire categories of entities, and for this reason they often co-occur with articles and adjectives.

Numerous neuropsychological studies have reported patients with significantly worse retrieval of proper nouns than common nouns, and a handful of studies also have documented the opposite dissociation (for reviews, see Rapp & Goldrick, 2006; Semenza, 2006, 2009). In at least one case, a selective deficit in both producing and comprehending the proper names of people has been traced to a highly circumscribed impairment at the level of concepts for unique individuals (Miceli et al., 2000; see also Gainotti, Spinelli, Scaricamazza, & Marra, 2008). More often, however, patients with greater difficulties retrieving proper than common nouns have fairly well-preserved knowledge of the referents of the intended words. Interestingly, for some of these patients the selective or disproportionate deficit in generating proper nouns relative to common nouns is restricted to just one modality of output, either speaking or writing (Cipolotti, MacNeil, & Warrington, 1993; Kemmerer, Tranel, & Manzel, 2005). And in keeping with the earlier discussion of patient M.M.L. (see Figures 30.1 & 30.2 and the associated text), such combined grammatical category-specific and output channel-specific disorders raise the intriguing possibility that proper nouns may be segregated from common nouns at the level of phonological and orthographic lexical forms. Further research is needed, however, to evaluate this hypothesis, since it is also possible that the two types of nouns are not systematically differentiated within each lexicon, but instead are accessed from distinct semantic subsystems via isolable projection pathways.

Turning to the brain, the neural basis of proper noun retrieval in oral picture-naming tasks has received a considerable amount of attention, and a sizable body of data from lesion studies, functional neuroimaging studies, and electrophysiological studies suggests that the left temporal pole plays an important role (for a review, see Tranel, 2009; see also Abel et al., 2015; Ross, McCoy, Coslett, Olson, & Wolk, 2011). In fact, there is growing evidence that this region is essential not only for naming famous faces, but also for naming famous voices (Waldron, Manzel, & Tranel, 2014), famous melodies (Belfi & Tranel, 2014), and famous landmarks (Gorno-Tempini & Price, 2001; Grabowski et al., 2001; Tranel, 2006; see Figure 30.5). The left uncinate fasciculus, which interconnects the temporal pole with the orbitofrontal cortex, has also been implicated in proper noun retrieval (Papagno et al., 2011, 2016), and so have several other regions, including the temporo-occipital cortex and the inferior frontal cortex (for a review, see Semenza, 2011; for fMRI data on the comprehension of proper versus common nouns, see Wang, Peelen, Han, Caramazza, & Bi, 2016).

Transitive versus Intransitive Verbs

Turning to the realm of verbal constructions, perhaps the most general distinction is between transitive and intransitive verbs (Dixon, 2010, Chapter 13). Transitive verbs designate events with two core participants, most often an "actor" and an "undergoer," with the actor being syntactically realized as a subject noun-phrase and the undergoer being syntactically realized as an object noun-phrase, at least in standard active-voice

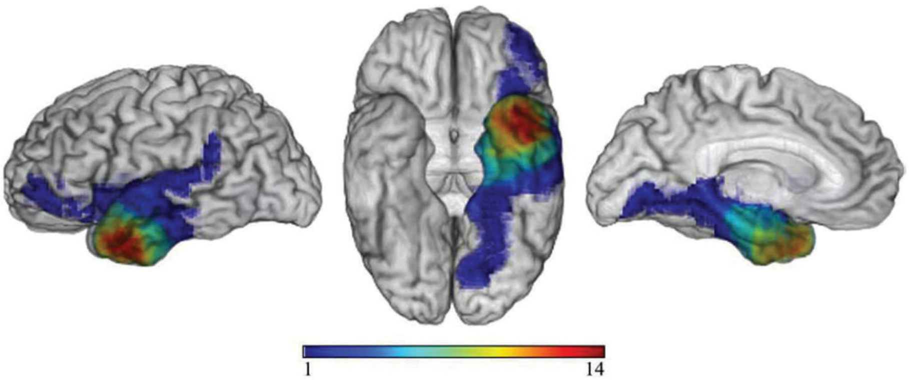

FIGURE 30.5. Lesion overlap map of patients with left temporal polar damage who have significantly impaired retrieval of proper nouns in tasks that require naming famous faces, voices, lankdmarks, and melodies. Images depict the overlap (from left to right) from the lateral perspective, ventral perspective, and mesial sagittal perspective. The "hotter" colors (orange to red) depict a higher number of lesion overlaps.

Source: Reproduced with permission from Waldron et al. (2014, p. 53). See also Belfi & Tranel (2014).

clauses (e.g., *The housewife kissed the mailman*). In contrast, intransitive verbs designate events with just one core participant, syntactically realized as a subject noun-phrase. Usually this participant is a volitional actor (e.g., *The mailman bolted*), but sometimes it is a passive undergoer (e.g., *The mailman blushed*). It all depends on the nature of the verb. Transitivity itself also depends, ultimately, on the lexical specifications of particular verbs, not the real-world properties of the designated events. For example, the general notion of "eating" is associated with the verbs *eat, devour*, and *dine*, but these three verbs exhibit different types of transitivity. The first verb, *eat*, is, technically speaking, ambitransitive, since it can be either transitive, as in *Bill ate the lasagna,* or intransitive, as in *Bill ate.* The second verb, *devour*, is strictly transitive, since one can say *Bill devoured the lasagna* but not **Bill devoured.* And the third verb, *dine*, is strictly intransitive, since one can say *Bill dined* but not **Bill dined the lasagna.* Despite these and other complications, there is still a strong overall tendency for two-participant verbs to be syntactically transitive and one-participant verbs to be syntactically intransitive.

Several neuropsychological studies have documented double dissociations between these two types of verbs, especially in production tasks. Worse retrieval of transitive than intransitive verbs appears to be the most common pattern (Cho-Reyes & Thompson, 2012; De Bleser & Kauschke, 2003; Kemmerer & Tranel, 2000; Kim & Thompson, 2000, 2004; Luzzatti et al., 2002; Thompson, Lange, Schneider, & Shapiro, 1997), but a few patients with the opposite performance profile have also been reported (Jonkers & Bastiaanse, 1998; Kemmerer & Tranel, 2000). As yet, very little is known about the lesion correlates of these kinds of deficits, but a few fMRI studies have begun to investigate the neural substrates of transitive and intransitive verbs in healthy subjects using a variety of both production and comprehension tasks (den Ouden, Fix, Parrish, & Thompson, 2009; Hernandez, Fairhall, Lenci, Baroni, & Caramazza, 2014; Thompson et al., 2007; see also Assadollahi, Meinzer, Flaisch, T., Obleser, & Rockstroh, 2009; Meltzer-Asscher, Schuchard, den Ouden, & Thompson, 2013). The findings obtained so far, however, are quite mixed. Some of the results suggest that transitive verbs depend more than intransitive verbs on the left temporoparietal cortex—in particular, the region extending from the pMTG/pSTS into the angular gyrus—as well as on Broca's area. Other results, though, paint a more complicated picture, with each verb class evoking rather heterogeneous patterns of activation. These inconsistencies may be related to the fact that the overarching classes of transitive and intransitive verbs are by no means monolithic, since each of them can be broken down into many fine-grained microclasses based on correspondences between semantic content and grammatical behavior (Levin, 1993). Hence it may be fruitful for future neurolinguistic research to take into account not only the general transitive-intransitive distinction, but also these more specific contrasts (Kemmerer, 2000a, 2003, 2014; Kemmerer & Wright, 2002; Kemmerer et al., 2008).

Beyond Nouns and Verbs

The multifarious morphological and syntactic constructions that comprise the grammatical systems of individual languages distinguish not only between (subclasses of) nouns and verbs, but also between numerous other grammatical categories (Croft, 2000, forthcoming; Culicover, 1999; Haspelmath, 2007; Pullum & Scholz, 2007; Taylor, 2012). None of these categories has received as much attention in neurolinguistics as nouns and verbs, but many of them have nevertheless been investigated in various ways.

In addition to nouns and verbs, most languages have two other open categories—namely, adjectives and adverbs (although the former category is sometimes closed, and the latter category is often ill-defined; see Dixon, 2010, Chapter 12). Adverbs have not yet been carefully studied in neurolinguistics, but some aspects of adjectives have begun to be explored. For example, when multiple adjectives are strung together before a noun, their linear order must conform to certain constraints that are primarily semantic in nature (Bache, 1978; Feist, 2011; Frawley, 1992; Quirk, Greenbaum, Leech, & Svartvik, 1985; Scontras, Degen, & Goodman, 2017). This is why it is fine to say *the other small inconspicuous carved jade idols* but not **the carved other inconspicuous jade small idols.* Interestingly, there is some evidence that brain damage—especially, but not exclusively, in Broca's area and/or the left inferior parietal lobule—can impair a person's knowledge of the positional restrictions on prenominal adjectives while leaving intact their knowledge of the idiosyncratic meanings of such adjectives (Kemmerer, 2000b; Kemmerer, Tranel, & Zdansczyk, 2009; see also Kemmerer, Weber-Fox, Price, Zdansczyk, & Way, 2007; Vandekerckhove, Sandra, & Daelemans, 2013). It is also noteworthy that in a recent neuropsychological study by Miozzo, Rawlins, and Rapp (2014), two patients with lesion overlap in the left IFG manifested thematic role confusions for comparative adjectival constructions (e.g., *The glove is darker than the hat*) and spatial prepositional constructions (e.g., *The box is in the bag*), but not for simple transitive constructions (e.g., *The woman helps the man*). These patterns of association and dissociation suggest that nonverbal word classes, particularly adjectives and prepositions, may recruit different brain mechanisms for thematic role assignment than verbal word classes, particularly transitive verbs.

Whereas open-class categories provide most of the conceptual content of utterances, closed-class categories have relatively austere meanings and contribute more to the structural organization of utterances (Talmy, 1988). Some English examples include articles like *a* and *the*; demonstratives like *this* and *that*; auxiliary and modal verbs like *do, have, can, could, may, might, must, ought, should, would*, and *will*; prepositions like *in, on, over, under, across, through, for, of, until, during*, and *since*; and conjunctions like *and, or, but, because, therefore, moreover*, and *however.* During receptive language processing, closed-class words elicit different electrophysiological waveforms than open-class words, even when the two types of lexical items are matched for frequency and length (Pulvermüller, Lutzenberger, & Birbaumer, 1995). Moreover, within the sphere of closed-class elements, different categories have distinct electrophysiological signatures (Weber-Fox, Hart, & Spruill, 2006). As described in the following, dissociations have also been found during language production tasks, not only between the two large-scale domains of open- and closed-class words, but also between different types of closed-class words.

Most of the relevant data come from the syndrome of agrammatism (Menn, O'Connor, Obler, & Holland, 1995; see Thompson & Mack, Chapter 31 in this volume). When attempting to formulate sentences, patients with this disorder can produce a wide range of open-class words, but they tend to have significant trouble generating closed-class words, with the majority of errors involving omissions. In addition, comparisons of the performance profiles of multiple patients have revealed a great deal of variability regarding both the kinds of closed-class words that are impaired and the degree to which they are affected. To take a rather striking example, consider preposition-particle homonyms that differ as to whether they are semantically or syntactically determined. In the sentence *She ran up the stairs*, the preposition *up* denotes a specific direction of motion, but in the sentence *She called up her friend*, the particle *up* is just an obligatory ingredient of the verb-particle expression *call up.* Not surprisingly, these two instances of *up* have different grammatical behaviors. Although it would be fine to say *Up the stairs she ran*, it would be very odd to say **Up her friend she called*, and conversely, one could never get away with **She ran the stairs up*, but there is nothing wrong with *She called her friend up*. Now, given such contrasts, it is especially interesting to note that semantically determined prepositions and syntactically determined particles can be impaired independently of each other by brain injury (Friederici, 1982; Friederici, Schönle, & Garrett, 1982; Kohen, Milsark, & Martin, 2011). This remarkable double dissociation suggests that the two types of closed-class words have at least partially separate neural substrates.

Agrammatism is most often manifested by patients with stroke-induced Broca's aphasia, but the lesions in such patients are quite diverse, variably affecting all of the major sectors of the large left perisylvian zone, with Broca's area sometimes being damaged and sometimes being spared (Vanier & Caplan, 1990). For these reasons, it has been challenging to use deficit-lesion correlations in agrammatic Broca's aphasics as a source of data about the neural underpinnings of closed-class items. On the other hand, agrammatism is also displayed by patients with progressive nonfluent aphasia, and the fact that their atrophy is typically centered in the left ventrolateral prefrontal territory provides some support for the view that Broca's area and the surrounding regions may actually be critically involved in the processing of closed-class items (Wilson et al., 2010). Further evidence for this view comes from a few PET and fMRI studies that have implicated Broca's area in some of the grammatical operations that take place during normal sentence production, including the generation of closed-class items (Haller, Radue, Erb, Grodd, & Kircher, 2005; Indefrey et al., 2001; Indefrey, Hellwig, Herzog, Seitz, & Hagoort, 2004). Much more research is needed, however, to elucidate the many similarities and differences in how various categories of closed-class words are implemented in the brain.

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CHAPTER 31

NEUROCOGNITIVE MECHANISMS OF AGRAMMATISM

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INTRODUCTION

AGRAMMATISM is a language disorder resulting from damage to the (usually) left hemisphere language network. The primary deficit seen in individuals with agrammatism is difficulty producing grammatical sentences. Individuals with agrammatism produce short, grammatically impoverished sentences or sentence fragments, consisting of primarily open class, content words with errors in grammatical morphology, for example, omission and/or substitution of verb inflection (Faroqi-Shah & Thompson, 2003; Saffran, Schwartz, & Marin, 1980; Thompson, Cho, et al., 2012). Consider the following narrative language sample from a 35-year-old male (L.B.S.) with chronic stroke-induced agrammatic aphasia, telling the story of Cinderella:

> She's nice. Dusting (3 sec). Wash (3 sec). The old man (4 sec). Wicked uh sisters uh two three five uh. The horse (5 sec) dog uh bird (3 sec) mouse uh uh is (3 sec) cut (11 sec) dress (2 sec). Be (4 sec) alright. Pumpkin. Pull over uh uh. The uh prince (2 sec). The love uh. We dance (2 sec). Oh no uh noon. How uh get out uh uh? Shoe uh glass shoe (5 sec) found its uh uh. Pulling (3 sec) shoe uh. No ties. Yes. The end.

Linguistic analysis of L.B.S.'s speech using a method developed by Thompson and colleagues (see Thompson, Cho, et al., 2012; Thompson, Shapiro, Li, and Schendel, 1995) revealed a greatly reduced speech rate (i.e., 14 words per minute; mean for healthy age-matched controls = 132.22; standard error of mean [SEM] = 5.22; data from Thompson, Cho, et al., 2012) and utterance length (mean = 2.37 words; mean for healthy controls = 11.11 [SEM = 0.56]). Only 10% of the patient's sentences were syntactically correct (healthy control mean = 93% [SEM = 1%]), with a complex-to-simple sentence ratio of .10. He also produced more open-class compared to closed-class words (open:closed-class ratio = 2.41; healthy control mean = 0.95 [SEM = 0.03]), with omission of matrix verbs and marked difficulty producing verb inflections (0% correct) (with noun inflection at 100% correct).

These patterns have been borne out in many experimental studies of language production in agrammatic aphasia caused by stroke. In constrained tasks, agrammatic speakers often show ability to produce simple active, canonical sentence structures; however, they show particular difficulty producing sentences with noncanonical word order (Caplan & Hanna, 1998; Cho-Reyes & Thompson, 2012; Faroqi-Shah & Thompson, 2003). Using the Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, 2011; also see Cho-Reyes and Thompson, 2012), which tests production of both canonical forms (i.e., actives, subject-*wh* questions, and subject-relative structures) and noncanonical forms (passives, object-*wh* questions, and object-relative constructions) using a sentence production priming task, we (Cho-Reyes & Thompson, 2012) documented this pattern in 35 patients with agrammatic aphasia with mild to moderately severe deficits. Mean production of canonical forms was 72% accurate, compared to a mean of 39% accuracy for noncanonical forms. Studies explicitly examining verb production in agrammatism also show deficits in both verb-naming and sentence-production tasks across languages, including English (Kim & Thompson, 2000; Thompson, Lange, Schneider, & Shapiro, 1997; Thompson, Lukic, King, Mesulam, & Weintraub, 2012; Zingeser & Berndt, 1990), German (De Bleser & Kauschke, 2003), Dutch (Bastiaanse, Hugen, Kos, & van Zonneveld, 2002), Hungarian (Kiss, 2000), Italian (Luzzatti et al., 2002), Russian (Dragoy & Bastiaanse, 2010), Korean (Sung, 2016), and Chinese (Bates, Chen, Tzeng, Li, & Opie, 1991).

Other work has shown that verb inflection is particularly vulnerable in agrammatism. Verb inflections such as subject-verb agreement (e.g., third-person singular present tense *-s* in English) and tense markings (e.g., English past tense *-ed*) are missing or incorrectly substituted in agrammatic speech (Arabatzi & Edwards, 2002; Bastiaanse et al., 2011; Burchert, Swoboda-Moll, & Bleser, 2005; Dickey, Milman, & Thompson, 2008; Druks, 2006; Faroqi-Shah & Thompson, 2007; Friedmann & Grodzinsky, 1997; J. Lee, Milman, & Thompson, 2008; Wenzlaff & Clahsen, 2004). In a study testing production of grammatical morphology (using the Northwestern Assessment of Verb Inflection; J. Lee & Thompson, 2017), participants with agrammatism produced fewer correct finite (tensed) verbs (i.e., 53% correct) compared to a group of participants with anomic aphasia (75% correct; Thompson, Meltzer-Asscher, et al., 2013). Similarly, function words such as auxiliaries (e.g., *be, have, do*) and complementizers (e.g., *if, that, whether*) are commonly absent (Arabatzi & Edwards, 2002; Friedmann & Grodzinsky, 1997; Milman, Dickey, & Thompson, 2008). Further, nominal functional morphemes such as possessive *-s* and the definite determiner *the* can be impaired (Wang, Yoshida, & Thompson, 2014). These patterns have been observed in English, as well as in typologically diverse languages such as German, Hebrew, and Japanese, and across tasks, including spontaneous speech, sentence completion, grammaticality judgment, repetition, and naming

(Burchert et al., 2005; Dickey et al., 2008; Friedmann, 2002; Friedmann & Grodzinsky, 1997; Hagiwara, 1995; Milman et al., 2008; Thompson, Meltzer-Asscher, et al., 2013; Wenzlaff & Clahsen, 2004).

Individuals with stroke-induced agrammatic aphasia also evince difficulty comprehending sentences, with particular difficulty understanding complex, noncanonical structures and semantically reversible forms (Caplan, Hildebrandt, & Makris, 1996; Caramazza & Zurif, 1976; Cho-Reyes & Thompson, 2012; Grodzinsky, 2000; Schwartz, Saffran, & Marin, 1980; and many others), where interpretation of "who did what to whom" cannot be derived from semantic or real-world knowledge alone. In one of the first studies of sentence comprehension in aphasia, Caramazza and Zurif (1976) showed that individuals with Broca's aphasia (and agrammatism) had problems understanding noncanonical, center-embedded sentences such as *the girl that the boy is pushing is blond*.

The most common cause of agrammatic aphasia is stroke within the distribution of the middle cerebral artery. Associated with Broca's aphasia, damage to anterior brain tissue (i.e., the left inferior frontal gyrus [IFG], Brodmann's areas 44 and 45, and adjacent tissue) is common, although research shows that lesions often extend well beyond this region and affect both gray matter and white matter (Cappa, 2012; Catani & Mesulam, 2008; Kertesz, Lesk, & McCabe, 1977; Lukic, Bonakdarpour, den Ouden, Price, & Thompson, 2014; Vanier & Caplan, 1990). Kertesz (1977), using radionucleide to examine lesions in 14 patients presenting with "low fluency associated with relatively well-preserved comprehension" (p. 594), showed that although the common area of infarction involved the IFG (in all patients except one), lesions extended to adjacent frontal as well as temporoparietal tissue. Data from our lab support this pattern. For example, in a recent study including 14 individuals with stroke-induced agrammatism, all participants had lesions in left hemisphere perisylvian regions, including inferior frontal and temporoparietal regions (see Figure 31.1). In addition, recent lesion-symptom mapping studies also implicate both anterior and posterior brain tissue in sentence comprehension and production impairments. For example, in a lesion-symptom mapping study that included 34 patients with stroke-induced aphasia, we (Lukic et al., 2014) found that lesions in anterior (IFG, insula) and posterior perisylvian regions (superior temporal gyrus [STG], angular gyrus [AG], and supramarginal gyrus [SMG]), as well as the arcuate fasciculus (a dorsal white matter tract), significantly predicted agrammatic production deficit patterns (i.e., impaired verb naming, verb-argument structure production, and production of complex sentences).

Agrammatism is also caused by neurodegenerative disease (i.e., primary progressive aphasia [PPA]; see Wilson, Chapter 2 in this volume). One variant of PPA is associated with grammatical deficits (i.e., the agrammatic variant [PPA-G] or nonfluent/agrammatic variant [naPPA]) (Gorno-Tempini et al., 2011; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Thompson & Mack, 2014; Wilson, Galantucci, Tartaglia, & Gorno-Tempini, 2012). We (Mesulam, Thompson, & colleagues; e.g., Mesulam et al., 2009; Mesulam et al., 2012; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013) use the term *PPA-G* to refer to patients with grammatical

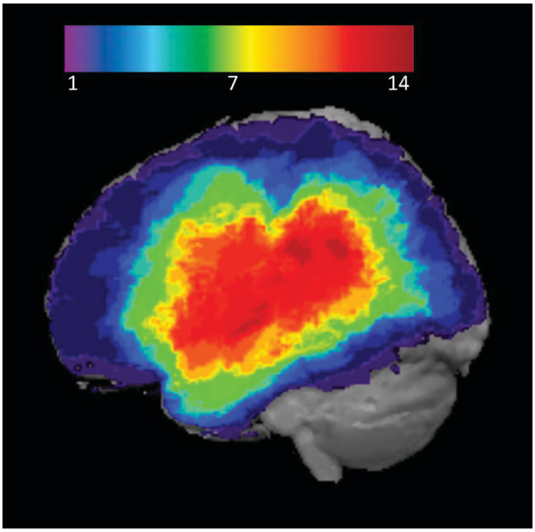

FIGURE 31.1. Lesion locations in 14 individuals with agrammatism enrolled in an ongoing study of the neural correlates of language recovery (Thompson lab, in progress). The color bar indicates the number of participants whose lesions overlap at each voxel. Peak areas of overlap (red) include left hemisphere anterior and posterior perisylvian regions, including the inferior frontal gyrus, superior temporal gyrus, and inferior parietal lobule.

impairments, rather than *naPPA*, since the latter requires one of two core features, either of which is sufficient for classification: (1) agrammatism in language production, and/or (2) motor speech deficits. Importantly, however, not all PPA patients with grammatical impairments present with motor speech difficulty, and patients with "pure" progressive motor speech deficits have been reported who do not evince grammatical impairments (Josephs et al., 2006; Mesulam et al., 2012; Rohrer, Rossor, & Warren, 2010; Wicklund et al., 2014; see Thompson & Mack, 2014, for review). Further, although nonfluent speech production is seen in patients with PPA-G, other variants of PPA also may show nonfluent speech (i.e., logopenic PPA (PPA-L), characterized by impaired word-finding and repetition with intact grammatical abilities), and some evince dissociations between fluency and grammatical ability (Thompson, Cho, et al., 2012). Furthermore, evidence is mixed regarding the degree of overlap between the neural substrates of fluency and grammatical production in PPA (Catani et al., 2013; Gunawardena et al., 2010; Mandelli et al., 2014; Rogalski et al., 2011; Wilson, Henry, et al., 2010).

Like stroke-induced agrammatism, patients with PPA-G show relatively spared single-word comprehension in the face of impaired grammatical ability in production and complex sentence comprehension impairments (Thompson, Cho, et al., 2012; Thompson & Mack, 2014; Thompson, Meltzer-Asscher, et al., 2013; Wilson et al., 2012). Quantitative analyses of speech samples have typically found more grammatical errors in PPA-G than in healthy age-matched controls or other variants of PPA (e.g., PPA-L, semantic PPA [PPA-S]) (Knibb, Woollams, Hodges, & Patterson, 2009; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010). Speakers with PPA-G produce fewer syntactically complex utterances (Ash et al., 2009; Gunawardena et al., 2010; Knibb et al., 2009; Wilson, Henry, et al., 2010) than do cognitively healthy controls. Some studies also show a trend toward higher open:closed (O:C) class ratios, with production of fewer verbs compared to nouns (Ash et al., 2009; Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997; Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010) in PPA-G compared to patients with other PPA subtypes. Finally, verb inflection errors (e.g., tense and agreement) in spontaneous language production are prevalent in PPA-G (Thompson, Cho, et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Henry, et al., 2010; also see Graham, Patterson, & Hodges, 2004).

In constrained production tasks, speakers with PPA-G also exhibit grammatical production impairments, particularly for syntactically complex, noncanonical sentences, whereas individuals with PPA-L and PPA-S show relatively unimpaired performance (Cupit et al., 2016; DeLeon et al., 2012; Thompson, Meltzer-Asscher, et al., 2013). We (Thompson, Meltzer-Asscher, et al., 2013) found that while speakers with PPA-G and PPA-L produce canonical sentences (e.g., active sentences, subject *wh*-questions, and subject-relative clauses) with comparable accuracy, accuracy is significantly lower in PPA-G than in PPA-L for noncanonical forms (e.g., passive sentences, object *wh*-questions, and object-relative clauses). In addition, verb-production deficits have been quantified in picture-naming tasks. Individuals with PPA-G exhibit more significant impairment in verb (action) naming than in noun (object) naming (Hillis et al., 2006; Hillis, Oh, & Ken, 2004; Hillis, Tuffiash, & Caramazza, 2002; Thompson, Lukic, et al., 2012). However, verb comprehension, like noun comprehension, is largely preserved in PPA-G (Hillis et al., 2006; Thompson, Lukic, et al., 2012). We (Thompson, Meltzer-Asscher, et al., 2013) also found, in a study testing verb inflection using the Northwestern Assessment of Verb Inflection (J. Lee & Thompson, 2017), that PPA-G speakers show greater difficulty producing finite compared to nonfinite verb inflection, suggesting a morphosyntactic locus of verb inflection deficits in this population. Impaired morphophonological processing also has been argued to contribute to verb inflection deficits in PPA-G (Wilson, Brandt, et al., 2014). Further, like agrammatism caused by stroke, PPA-G is associated with deficits in comprehension of syntactically complex sentences (Cooke et al., 2003; Gorno-Tempini et al., 2011; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Dronkers, et al., 2010).

Studies measuring cortical thickness in people with PPA-G (compared to cognitively healthy people) show peak atrophy in the left hemisphere IFG, although atrophy is also observed in left hemisphere premotor, dorsolateral prefrontal, and posterior temporoparietal regions in both early and later stages of disease (Mesulam et al., 2009; Mesulam et al., 2012) (see Figure 31.2). Atrophy in the left IFG has been associated with a range of features of agrammatism, including impaired complex sentence comprehension (Amici et al., 2007; Peelle et al., 2008; Wilson et al., 2011) and production (DeLeon et al., 2012; Gunawardena et al., 2010; Rogalski et al., 2011; Wilson et al., 2011; Wilson, Henry, et al., 2010). In addition, agrammatism in PPA is associated with damage to

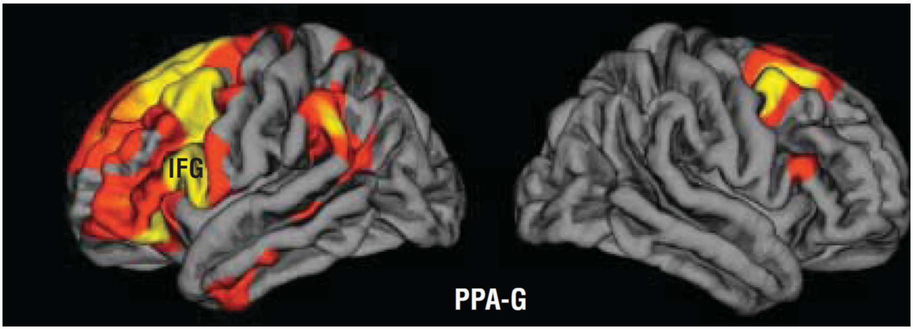

FIGURE 31.2. Sites of cortical atrophy in agrammatic PPA (PPA-G). Orange and yellow areas showed significant atrophy as compared to age-matched controls. Areas of peak atrophy (yellow) in the left hemisphere include the inferior frontal gyrus (IFG), the temporoparietal junction, and premotor and dorsolateral prefrontal regions.

Source: Mesulam et al. (2009).

white matter tracts in the left hemisphere (e.g., anterior, posterior and long segments of the arcuate) (Catani et al., 2017; Wilson et al., 2011), as in agrammatism caused by stroke.

This chapter is focused on sentence production and comprehension deficits associated with agrammatism, with emphasis on the neurocognitive mechanisms underlying these impairments. Grammatical sentence processing engages lexical as well as morphosyntactic processes. Within the lexical domain, verb processing is particularly germane, since verbs encode syntactic information (i.e., subcategorization frames) as well as verb-argument or event structure (i.e., participant roles entailed within the verb's representation; see Kemmerer, Chapter 30 in this volume). Thus, verb-argument structure is considered an interface between semantics (e.g., who did what to whom) and syntax (e.g., word order) and is essential for production and comprehension of simple monoclausal sentences, as well as complex syntactic structures, which contain embedded clauses and/or noncanonical argument order (e.g., passive sentences such as *The girl was kissed by the boy*, in which the Theme argument precedes the Agent). Following many theoretical linguistic models, we assume a "lexicalist" approach in which verb-argument structure guides phrase structure building, which, in turn, mediates sentence processing (Caramazza, 1997; Chomsky, 1981; Horvath & Siloni, 2011; Jackendoff, 1972; Levelt, Roelofs, & Meyer, 1999; Levin & Rappaport, 1986; Reinhart, 2002; Williams, 1981; but see Goldberg, 1995, 2003, for discussion of the "constructivist" approach, which argues that verb-argument structure is strongly tied to semantics). The next section of this chapter discusses verb and verb-argument structure impairments seen in agrammatic aphasia as they relate to sentence comprehension and production abilities. This is followed by discussion of studies examining complex sentence processing in agrammatism. Then, we address neurocognitive mechanisms associated with verb and sentence impairments. Throughout, based on the extant literature, we discuss theories of agrammatism with a focus on impaired thematic integration (i.e., the processes that support the licit combination of a verb's thematic roles and its constituent arguments to yield the intended meaning of a sentence).

VERB AND VERB-ARGUMENT STRUCTURE DEFICIT PATTERNS

Verbs are used to describe different types of events, with different numbers and types of core participants (arguments). For example, some verbs are predominantly used to describe events with one core participant (e.g., *swim*), whereas others describe events with two (*lift*) or three (*give*) core participants. Further, the meanings of verbs select for different sets of thematic roles, encoding the roles that participants play in the event. For example, events described by *lift* typically encode an Agent and Theme (e.g., *John lifted the box*), whereas events described by *amuse* typically encode a Theme and an Experiencer (e.g., *The show amused John*). On many current accounts, these thematic role labels are a convenient stand-in for a more elaborated lexical-conceptual structure that represents the relationships between event participants (e.g., Levin & Rappaport Hovav, 2005). Verbs also differ with respect to the constraints they place on the syntactic realization of their arguments (subcategorization frames). For example, *discover* allows both nominal and sentential complements (*They discovered the new drug; They discovered that the new drug was effective*) whereas *produce* only allows nominal complements (*They produced the new drug*). We refer to the semantic and syntactic requirements of verbs as *verb-argument structure*.

Many studies suggest that the representation of verb meaning and verb-argument structure is intact in agrammatism. The evidence for this view has come from a range of experimental paradigms, including single-word comprehension, cross-modal lexical decision, grammaticality judgments, and structural priming. Agrammatic individuals' single-verb comprehension is often preserved (but see Miceli, Silveri, Nocentini, & Caramazza, 1988), with no deficits in comprehending verbs with complex argument structures (Kim & Thompson, 2000, 2004; M. Lee & Thompson, 2004; Piñango, 2000; Thompson, Lukic, et al., 2012). Agrammatic speakers also show normal access to subcategorization frames during online sentence processing. As in non-brain-damaged volunteers, reaction times (RTs) are longer for verbs with multiple subcategorization options versus those with only one such option, reflecting exhaustive online access to argument structure representations (Shapiro, Gordon, Hack, & Killackey, 1993; Shapiro & Levine, 1990). Access to information about the relative frequencies of different subcategorization frames also appears to be intact (DeDe, 2013a, 2013b). Individuals with agrammatism also evince relatively preserved ability to distinguish sentences with correct argument structure (e.g., *The boy is carrying the girl; The dog is barking*) from argument structure violations, such as argument omission (e.g., **The boy is carrying*) and argument insertion (e.g., * *The dog is barking the girl*) (Grodzinsky & Finkel, 1998; Kim

& Thompson, 2000, 2004; though see Kielar, Meltzer-Asscher, & Thompson, 2012), indicating intact access to sentence-level argument-structure representations. They also show intact priming of the order of thematic roles in sentence production, supporting the view that argument structure representations are intact (Cho-Reyes, Mack, & Thompson, 2016).

However, despite apparently intact argument structure representations, some aspects of the online processing of verbs and verb-argument structure are impaired. Individuals with agrammatism caused by stroke have demonstrated impaired online responses to argument-structure violations (e.g., **John sneezed the doctor*), including abnormal event-related potential (ERP; see Leckey & Federmeier, Chapter 3 in this volume) signals (Kielar et al., 2012), and reaction times (Myers & Blumstein, 2005). In contrast with healthy adults, they also show deficits in using the verb's selectional restrictions (e.g., that *eat* requires an edible direct object, but *move* does not) to predict and integrate arguments (Mack, Ji, & Thompson, 2013; cf. Dickey & Warren, 2015, who report impaired online verb-argument integration in a group of four individuals with stroke-induced aphasia, two of whom have Broca's aphasia). In PPA-G, two studies have revealed impaired online processing of verb-argument structure violations, one using ERP (Barbieri et al., 2016) and one using reaction-time measures (Peelle, Cooke, Moore, Vesely, & Grossman, 2007); however, one study found intact online processing of these violations (Price & Grossman, 2005). Further, our preliminary research shows impaired verb-argument prediction in listeners with PPA-G (Mack, Mesulam, & Thompson, 2017). Overall, the picture that emerges is that agrammatic individuals' representation of verb meaning and verb-argument structure seems to be spared, but thematic (i.e., verb-argument) integration is impaired, as shown by abnormal online responses to violations and impaired prediction.

Verb retrieval and verb-argument structure processing is, however, impaired in production. Speakers with agrammatism caused by stroke and PPA produce frequent verb-argument structure errors in structured tasks and in spontaneous language production (Thompson, Ballard, et al., 1997; Thompson, Cho, et al., 2012; Thompson, Lange, et al., 1997; Thompson et al., 1995). Several studies have shown that argument structure complexity affects verb retrieval and sentence-production accuracy. Notably, the literature on argument-structure complexity in agrammatism encompasses typologically diverse languages including English (Thompson, 2003), Dutch (Bastiaanse & van Zonneveld, 2005), German (De Bleser & Kauschke, 2003), Greek (Stavrakaki, Alexiadou, Kambanaros, Bostantjopolou, & Katsarou, 2011), Hungarian (Kiss, 2000), Italian (Luzzatti et al., 2002), Russian (Dragoy & Bastiaanse, 2010), and Korean (Sung, 2016).

Argument number is one relevant factor that shapes verb production in agrammatism; for example, two- and three-argument verbs (e.g., *lift, give*) are named less accurately than one-argument verbs (e.g., *swim*) (Kim & Thompson, 2000, 2004; Kiss, 2000; Luzzatti et al., 2002; Sung, 2016; Thompson, Lange, et al., 1997; Thompson, Lukic, et al., 2012). These effects are shown in both stroke-induced agrammatism and PPA-G (Thompson, Lukic, et al., 2012). The number of arguments selected by the verb also affects both structured sentence production tasks and narrative production: two- and three-argument sentences are produced less frequently and/or accurately than in unimpaired speakers (Bastiaanse & Jonkers, 1998; De Bleser & Kauschke, 2003; Dragoy & Bastiaanse, 2010; Thompson, Lange, et al., 1997). Related to this, a recent study examined the verb's number of subcategorization frames (i.e., complement types) as a potential factor affecting aphasic sentence production in narratives (Malyutina, Richardson, & den Ouden, 2016). In this study, speakers with Broca's aphasia produced verbs with fewer arguments and less diverse subcategorization frames, consistent with the idea that thematic integration is impaired in production.

In addition, agrammatism is associated with deficits in producing unaccusative verbs, that is, one-argument verbs in which the grammatical subject is assigned the Theme role (e.g., *The man* ***fell***; first described by Perlmutter, 1978), in contrast with unergative verbs, which have an Agent subject (e.g., *The man* ***swam***). These deficits have been observed in verb naming (Luzzatti et al., 2002; Sung, 2016; Thompson, 2003) and in sentence production (Bastiaanse & van Zonneveld, 2005; Dragoy & Bastiaanse, 2010; Kegl, 1995; M. Lee & Thompson, 2004; Stavrakaki et al., 2011), and have been argued to reflect the syntactic and thematic complexity of unaccusatives. Syntactically, unaccusatives (on some models of grammar, such as Government and Binding; Chomsky, 1981) involve a movement operation, in which the Theme argument moves from an underlying object position to the subject position (*The man*$_i$ *fell* __$_i$) (Burzio, 1986; Levin & Rappaport Hovav, 1995). Unaccusatives are also complex (and noncanonical) in terms of the mapping from thematic roles to syntax, given that the subject is assigned the Theme role. Similarly, object-experiencer verbs (e.g., *The woman shocked the man*) also contain a noncanonical argument order (subject = Theme; object = Experiencer) and have been argued to involve syntactic movement (Belletti & Rizzi, 1988). These have been shown to be impaired in agrammatic speakers (Thompson & Lee, 2009).

A distinct line of research has examined the effect of "semantic weight" on verb production in aphasia. This research contrasts production of semantically "heavy" verbs (e.g., *bake*), which have a clear and specific meaning, to semantically "light" verbs (e.g., *get*), which have a vaguer meaning and can appear in a variety of contexts. This research has demonstrated that agrammatism is associated with differential impairment of light verbs (Gordon & Dell, 2003; Thorne & Faroqi-Shah, 2016). According to the Division of Labor Hypothesis (Gordon & Dell, 2003), this is due to the complex argument structures and subcategorization frames associated with light verbs (e.g., *get* can appear in a wide range of syntactic contexts, e.g., *get married, get to the party, get upset, get a haircut*). In certain contexts, light verbs also require online composition of argument structure. For example, in a sentence such as *John gave Bill an order to leave*, the argument structures of *give* and *order* must be combined to yield the sentence's interpretation, a process that is costly in typical language processing (Piñango, Mack, & Jackendoff, 2006; Wittenberg, Paczynski, Wiese, Jackendoff, & Kuperberg, 2014; Wittenberg & Piñango, 2011). Thus, impaired production of light verbs in agrammatism may also relate to difficulty with complex argument structures.

SENTENCE-PROCESSING DEFICITS IN AGRAMMATISM

As mentioned in the introduction to this chapter, agrammatism is also associated with impairments in comprehending and producing complex syntactic structures, including sentences with embedding and/or a noncanonical order of arguments (see Bornkessel-Schlesewsky & Schlesewsky, Chapter 27 in this volume). This has been found in agrammatism caused by stroke (Bastiaanse & van Zonneveld, 2005; Burchert, Meissner, & De Bleser, 2008; Cho-Reyes & Thompson, 2012; Dragoy & Bastiaanse, 2010; Llinas-Grau & Martinez-Ferreiro, 2014; Thompson, Meltzer-Asscher, et al., 2013) and in PPA-G (Cupit et al., 2016; DeLeon et al., 2012; Thompson, Meltzer-Asscher, et al., 2013; Wilson, Dronkers, et al., 2010; Wilson, Henry, et al., 2010). Several theoretical accounts have been proposed of these deficits, which vary with respect to whether deficits are attributed to damaged linguistic representations, deficits in specific aspects of linguistic processing, or a general reduction in processing capacity (see recent reviews in Bastiaanse & Jonkers, 2012; Caplan, 2012; Druks, 2017; and Patil, Hanne, Burchert, De Bleser, & Vasishth, 2016).

One major focus of research has been to explain impaired comprehension of noncanonical sentences with long-distance dependencies (e.g., *It was the girl$_i$ who$_i$ the boy kissed ___$_i$ that day at school*). On some linguistic theories, these structures involve movement of a syntactic constituent (e.g., the relative pronoun *who*) from its original post-verbal position, leaving behind a gap or trace (___$_i$) (Chomsky, 1981). In psycholinguistic terms, the *filler* (e.g., *who*, co-indexed with *the girl*) must be associated with the gap site (___$_i$), or with its subcategorizing verb (e.g., *kissed*), in order to be assigned the correct thematic role (e.g., Theme) (Frazier, Clifton, & Randall, 1983; Pickering & Barry, 1991). Association of the filler with the gap site (or verb) involves reactivating aspects of the representation of the filler that have decayed since its original presentation (e.g., semantic representation; see review in Wagers & Phillips, 2014).

Some accounts have attributed impaired comprehension of these structures in agrammatism to impaired representation of syntactic movement (Grodzinsky, 1986, 2000). If correct, this hypothesis would predict the absence of reactivation of the meaning of the filler at the gap site. Studies of online processing have primarily tested this hypothesis using two methods: cross-modal priming, where reactivation is indicated by priming effects for the filler at the gap site, and visual-world eye-tracking, where reactivation is indicated through an increase in eye movements to a picture of the filler at the gap site. Although some early cross-modal priming studies found impaired filler-gap processing in agrammatism (Swinney, Zurif, Prather, & Love, 1995, 1996; Zurif, Swinney, Prather, Solomon, & Bushell, 1993), the majority of more recent priming and eye-tracking studies found intact filler-gap reactivation effects, albeit at a delay in some studies (Blumstein et al., 1998; Burkhardt, Piñango, & Wong, 2003; Dickey, Choy, & Thompson, 2007; Dickey & Thompson, 2009; Love, Swinney, Walenski, & Zurif, 2008; Thompson & Choy, 2009). Further, eye-tracking experiments conducted in our lab indicated intact processing in other types of long-distance dependencies, such as pronouns and reflexives (Choy & Thompson, 2010; Hsu & Thompson, 2014; Thompson & Choy, 2009), with no evidence of disrupted syntactic representation (contra, e.g., Grodzinsky, Wexler, Chien, Marakovitz, & Solomon, 1993).

Processing accounts of sentence comprehension deficits in agrammatism assume intact syntactic representations, but impaired processing of linguistic information. The Derived Order Problem Hypothesis (DOPH; Bastiaanse & van Zonneveld, 2006) agrees with researchers such as Grodzinsky (1986, 2000) that syntactic movement is the source of agrammatic comprehension deficits, but suggests that these deficits are processing based rather than representational. In contrast, other accounts suggest that processing slowdowns lead to comprehension deficits; specifically, slowed lexical activation (Love et al., 2008) or syntactic processing (Burkhardt et al., 2003) leads to the overuse of default sentence-interpretation strategies (e.g., subject = Agent). A third type of processing account suggests that a general reduction of processing resources leads to slowdowns and "intermittent deficiencies" (i.e., inconsistent syntactic operations; Caplan, Waters, DeDe, Michaud, & Reddy, 2007; Hanne, Sekerina, Vasishth, Burchert, & De Bleser, 2011).

We have argued that sentence comprehension deficits relate to impaired thematic integration (Mack et al., 2013; Mack & Thompson, 2017; Meyer, Mack, & Thompson, 2012; Thompson & Choy, 2009). This work follows the Mapping Hypothesis (Linebarger, Schwartz, & Saffran, 1983; Schwartz, Linebarger, Saffran, & Pate, 1987) in proposing a deficit in mapping between thematic and syntactic structure. However, our work also attempts to identify the specific processes that break down online during thematic integration. The relevant processes include *thematic prediction* and *thematic role assignment*.

As sentences unfold in real time, unimpaired listeners predict upcoming words and structures, supporting sentence comprehension by reducing time and resources needed for lexical and/or structural processing (Federmeier, 2007; Kamide, 2008; Kutas, DeLong, & Smith, 2011; Van Petten & Luka, 2012). In the domain of thematic processing, unimpaired listeners predictively assign the Agent role to sentence-initial animate noun phrases, in the absence of disambiguating grammatical (e.g., case) information (Hanne, Burchert, De Bleser, & Vasishth, 2015; Kamide, Scheepers, & Altmann, 2003; Knoeferle, Crocker, Scheepers, & Pickering, 2005; Meyer et al., 2012). For example, upon hearing a sentence starting with *The woman*, unimpaired listeners predict that the woman will be assigned the Agent role—a correct prediction if the sentence turns out to be active (e.g., *The woman lifted the man*), but incorrect if it is passive (e.g., *The woman was lifted by the man*). Notably, recent eye-tracking work in our lab and others' shows that Agent-first predictions are absent in agrammatic listeners (Hanne et al., 2015; Mack & Thompson, 2017; Mack, Wei, Gutierrez, & Thompson, 2016; Meyer et al., 2012). Furthermore, restoring thematic prediction seems to be important for recovery of sentence comprehension in agrammatism. In a recent study, we used eye-tracking to examine changes in online sentence processing resulting from a course of language treatment in 10 individuals with agrammatism (Mack & Thompson, 2017). The language treatment protocol (Treatment of Underlying Forms [TUF]; Thompson & Shapiro, 2005) trained the production and comprehension of passive sentences. Although thematic prediction was not explicitly trained, participants nevertheless made more predictive eye movements following treatment. Further, the participants who showed greater increases in thematic prediction also showed greater improvement in sentence-comprehension accuracy.

In addition, thematic role assignment at the verb appears to be impaired in noncanonical sentences. For example, consider an object-cleft such as *It was the girl*$_i$ *who*$_i$ *the boy kissed* __$_i$ *that day at school.* Correct interpretation of this sentence requires assigning the boy the Agent role and the girl the Theme role (through its co-indexation with the gap and the relative pronoun *who*). As mentioned earlier, the majority of studies conducted to date suggest that agrammatic listeners can successfully compute the syntactic dependency, reactivating the filler (*who* = *the girl*) at the gap site. However, interpretation of the sentence is often incorrect, suggesting a subsequent failure to assign thematic roles correctly. Eye-tracking evidence is consistent with this hypothesis. For example, Dickey et al. (2007) found that listeners with agrammatism evinced eye movements indicative of successful syntactic dependency formation in object-*wh* questions, in sentences that were comprehended correctly as well as those comprehended incorrectly (cf. Dickey & Thompson, 2009; Thompson & Choy, 2009). In other words, syntactic dependency formation was generally successful, but thematic role assignment sometimes failed. Choy and Thompson (2010) reported a similar pattern of results in the processing of long-distance dependencies involving pronouns and reflexives: intact reactivation of the antecedent online, combined with impaired comprehension accuracy. Subsequent eye-tracking studies used a sentence-picture matching paradigm to probe incremental thematic role assignment during sentence comprehension. In sentences that were comprehended incorrectly, eye movements indicated aberrant thematic role processing throughout the sentence (Hanne et al., 2015; Hanne et al., 2011; Mack & Thompson, 2017; Mack et al., 2016; Meyer et al., 2012). These findings suggest that impaired thematic prediction and thematic role assignment play a key role in agrammatic comprehension deficits, leading to the Thematic Integration Hypothesis.

Moving to sentence production, some accounts propose that damage to syntactic representations underlies impairments in producing complex structures (Friedmann & Grodzinsky, 1997). However, as in sentence comprehension, there is evidence from sentence production that syntactic representations are intact. For example, agrammatic speakers show intact structural priming of complex structures; that is, they often use grammatical structures to which they have been recently exposed. This has been found for complex structures such as datives (Cho-Reyes et al., 2016; Hartsuiker & Kolk, 1998), passives (Cho & Thompson, 2010; Hartsuiker & Kolk, 1998), and cliticization in Italian (Rossi, 2015). Intact structural priming effects for complex structures also have been found in mixed groups of aphasic patients including agrammatic speakers (Saffran & Martin, 1997; Verreyt et al., 2013). Further, structural priming boosts production of complex structures in agrammatism. In one study (Cho-Reyes et al., 2016), 13 agrammatic speakers showed impaired production of dative sentences in isolation; however, in the context of a structural priming task, 7 of 13 speakers showed dative production accuracy within the normal range. These findings indicate that the representations of complex structures are intact.

Processing accounts vary with respect to the source of complex sentence production deficits. The Derived Order Problem Hypothesis, described earlier in the context of sentence comprehension, has also been applied to agrammatic production (Bastiaanse & van Zonneveld, 2005). This account claims that deficits stem from difficulty producing sentences with moved constituents. Other accounts propose more general processing impairments, such as a reduced sentence-planning window that poses difficulty for the production of complex sentences (Kolk, 1995). In contrast, we hypothesize that agrammatic speakers have difficulty with thematic integration during sentence production, which affects levels of processing including *lexical selection, grammatical function assignment*, and *morphosyntactic encoding* (see the model of Bock & Levelt, 1994) as well as the time course of *sentence-production planning*.

Lexical selection involves accessing and selecting lexical items (lemmas, containing semantic and syntactic but not phonological information) that encode an event's meaning, including the action (typically a verb) and the event participants (typically nouns). Accessing a verb lemma activates its argument structure, including its thematic roles (e.g., Agent, Theme). As described in the previous section, research in our lab and others' indicates that access to verbs with complex argument structures is particularly difficult for agrammatic speakers (e.g., Thompson, 2003). Grammatical function assignment concerns the mapping of selected lemmas to grammatical functions (subject, object). This process is guided by the argument structure information contained within verb lemmas: for example, some psychological verbs map the Experiencer to the subject role (e.g., *John enjoyed the show*) and others to the object role (e.g., *The show amused John*). Agrammatic speakers have deficits in using thematic information during grammatical function assignment, as reflected by difficulty in producing canonical active sentences with complex argument structures, such as two- and three-argument sentences (see previous section; e.g., Cho-Reyes & Thompson, 2012), as well as sentences with noncanonical argument order (discussed further in the following).

Morphosyntactic encoding refers to the generation of a hierarchically organized syntactic structure with morphologically specified words. The interplay between lexical selection, grammatical function assignment, and morphosyntactic encoding is especially important for complex sentence production. For example, to produce a passive sentence such as *The man was lifted by the woman*, the speaker must access the verb *lift* and its argument structure, map the Theme to the grammatical subject role and the Agent to an adjunct role, and select the correct morphosyntactic form of the verb (i.e., auxiliary + past participle). Establishing the relationship between grammatical function assignment and morphosyntactic encoding seems to be difficult for agrammatic speakers. When they are primed with the morphosyntactic structure of passives, they often produce role-reversal errors (i.e., incorrect grammatical function assignment; e.g., *The woman was lifted by the man*; Cho & Thompson, 2010) and when provided with a cue to map the Theme as the grammatical subject, they often produce morphosyntactic errors (e.g., *The man was lifting by the woman*; Faroqi-Shah & Thompson, 2003).

Further, agrammatic speakers often show abnormal sentence-planning processes, relating to impaired thematic integration. Two sentence-production planning modes have been observed in healthy speakers: *verb-based structural planning*, in which the speaker initially accesses the verb and uses it to build a structural frame that guides grammatical function assignment, and *word-by-word incremental planning*, in which the speaker first retrieves the most accessible noun and links it to the grammatical subject function. Healthy speakers use both modes of planning, depending on task demands and linguistic factors (Hwang & Kaiser, 2014; Kempen & Huijbers, 1983; J. Lee & Thompson, 2011a, 2011b; Schriefers, Teruel, & Meinshausen, 1998). Our preliminary work suggests that, unlike typical speakers, agrammatic speakers consistently retrieve verb information before speech onset, indicating verb-based structural planning (J. Lee & Thompson, 2011a, 2011b; J. Lee, Yoshida, & Thompson, 2015). For example, in two eye-tracking studies, speakers with agrammatism showed effects of argument structure complexity (e.g., encoding unaccusative vs. unergative verbs) before speech onset, whereas unimpaired speakers did so after speech onset (J. Lee & Thompson, 2011a, 2011b). This suggests a reliance on early retrieval of verb-argument structure information in agrammatic speakers, which is used to guide sentence planning (cf. J. Lee et al., 2015).

The use of structural planning may help agrammatic speakers manage the demands of sentence production, by temporally separating the costly processes of structural planning and articulation. However, faulty structural planning—that is, deficits in verb retrieval and mapping from thematic roles to syntactic structures—contribute to sentence-production deficits. In a recent eye-tracking study with nine agrammatic speakers (Mack, Nerantzini, & Thompson, 2017), we found evidence of abnormal structural planning during passive sentence production. However, after a course of Treatment of Underlying Forms (Thompson & Shapiro, 2005), which successfully trained passive sentence production, the agrammatic speakers showed more normal-like online sentence planning, reflecting improved thematic integration.

Neural Substrates of Verb- and Sentence-Processing Impairments in Agrammatism

Damage to left hemisphere frontal regions, posterior perisylvian regions, and dorsal white matter tracts have been consistently associated with agrammatism. In this section, we review the relevant findings regarding the neural substrates of verb- and sentence-processing impairments in agrammatism, situating them in the context of contemporary models of the neurobiology of language. We first discuss models of verb and verb-argument structure processing and follow this with sections on the neural mechanisms of sentence comprehension and sentence production, respectively.

Relatively few models have specifically addressed the neural substrates of verb and verb-argument structure processing. Thompson and Meltzer-Asscher (2014) proposed a model in which retrieval and integration of verb and verb-argument information is supported by a network consisting of left inferior parietal, posterior temporal, and inferior frontal regions. Early studies on stroke-induced aphasia suggested that verb-specific production deficits were related to left inferior frontal lesions, whereas noun-specific impairments were related to left temporal lesions (e.g., Damasio & Tranel, 1993; see review in Cappa & Perani, 2003; see also Kemmerer, Chapter 30 in this volume). However, more recent studies have shown that the neural substrates of verb-specific production deficits are more variable across individuals, and include lesions in left frontal, posterior temporal, and inferior parietal cortical regions, as well as damage to the insula, frontal operculum, dorsal white matter tracts, and/or subcortical structures such as the basal ganglia (e.g., Aggujaro, Crepaldi, Pistarini, Taricco, & Luzzatti, 2006; Kemmerer, Rudrauf, Manzel, & Tranel, 2012; Lukic et al., 2014; Piras & Marangolo, 2007; see reviews in Crepaldi, Berlingeri, Paulesu, & Luzzatti, 2011; Matzig, Druks, Masterson, & Vigliocco, 2009). Using voxel-based lesion symptom mapping (VLSM; Bates et al., 2003), we (Lukic et al., 2014) investigated the lesion locations associated with impaired production of argument structure. Impaired verb naming, measured with the Verb Naming Test of the Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, 2011), was associated with lesions in the left IFG, STG, and insula; these effects were numerically stronger for transitive than for intransitive verbs, suggesting that these regions support the retrieval of verbs with complex argument structures. Further, we examined the neural correlates of impairments on the Argument Structure Production Test (ASPT) of the NAVS. In this task, participants viewed action pictures with the verb and event participants labeled (e.g., *mail, man, letter*) and were asked to produce a grammatical sentence to describe the picture, which requires mapping the arguments of the verb to the correct grammatical functions. Impaired performance on the ASPT was associated with damage to the SMG and arcuate fasciculus (AF). In PPA, few studies have directly examined the neural correlates of verb retrieval deficits. In recent work, we found that impaired verb-argument structure production on the ASPT is correlated with atrophy in the left inferior parietal lobule in a large group of patients with PPA (Europa, Mack, Rogalski, Mesulam, & Thompson, in preparation). In line with the model proposed by Thompson and Meltzer-Asscher (2014), these findings strongly suggest that dorsal pathways (i.e., linking posterior temporal, inferior parietal, and inferior frontal regions via the AF) play an important role in impaired production of verbs and verb-argument structure.

Sentence comprehension impairments in agrammatism are predominantly observed in semantically reversible and syntactically complex (e.g., noncanonical) sentences. Several studies have attempted to localize the brain damage associated with comprehension impairments of this nature. In the literature on chronic agrammatism resulting from stroke, this has resulted in mixed findings. One large-scale study of 79 patients found that impaired comprehension of semantically reversible sentences was associated with lesions in left posterior perisylvian regions, specifically the AG, SMG, and posterior STG (Thothathiri, Kimberg, & Schwartz, 2012). Greater impairment of noncanonical versus canonical sentences was associated with lesions in the left AG. Another large (72-patient) study related lesion location to comprehension of sentences that varied with respect to reversibility and complexity (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). In that study, lesions in the anterior STG, AG, and left frontal regions anterior to Broca's area (BA 47 and BA 46) were associated with impaired sentence comprehension. Further, Caplan and colleagues observed relationships between syntactic complexity effects and lesions in the left posterior STG and AG, but not the IFG (Caplan, Michaud, Hufford, & Makris, 2016). These relationships were task- and structure-specific, suggesting that posterior perisylvian regions have distinct roles in carrying out syntactic operations in the contexts of particular tasks. In contrast, two previous studies by Caplan and colleagues found no significant relationships between lesion location and syntactic complexity effects on sentence comprehension (e.g., relatively impaired comprehension of passives vs. actives; Caplan et al., 1996; Caplan, Waters, Kennedy et al., 2007).

Further, a few studies have suggested that stroke-induced damage to the left IFG contributes to impaired predictive processing, which is important for sentence comprehension (Federmeier, 2007; Kamide, 2008; Kutas et al., 2011; Van Petten & Luka, 2012). In one study, clinically non-aphasic stroke survivors with left IFG lesions showed impaired prediction of morphosyntactic information (Jakuszeit, Kotz, & Hasting, 2013). In another study, aphasic individuals with left IFG lesions (but intact posterior perisylvian regions) showed impaired prediction of lexical-semantic and morpho-phonological information, whereas those with left posterior perisylvian lesions (but intact frontal regions) showed intact prediction (Nozari, Mirman, & Thompson-Schill, 2016). Similarly, we found that nine individuals with agrammatism and lesions that included left frontal regions showed impaired lexical-semantic prediction (Mack et al., 2013). These findings suggest that the left IFG supports linguistic prediction across domains. In future work, it will be important to test whether damage to this region is associated with impaired thematic prediction, which may contribute to deficits in sentence comprehension in agrammatism (Mack et al., 2013; Mack & Thompson, 2017; Mack et al., 2016; Meyer et al., 2012).

Studies conducted with PPA patients largely support those derived from stroke-induced aphasia. One large-scale study of 72 PPA patients found that impaired comprehension of semantically reversible, noncanonical sentences was associated with cortical atrophy in the left IFG, dorsal premotor cortex (DPM), and inferior parietal lobule (AG and SMG) (Mesulam, Thompson, Weintraub, & Rogalski, 2015). Generally consistent with this, another study reported an association between syntactic complexity effects (i.e., canonical>noncanonical difference scores) and atrophy in left frontal regions (IFG, DPM, and precentral gyrus [PCG]) as well as posterior temporal regions (left STG, middle temporal gyrus [MTG] and superior temporal sulcus [STS]) (Wilson, Dronkers, et al., 2010). A third study found an association between overall sentence comprehension impairment and atrophy in left posterior perisylvian regions, as well as a more specific association between deficits in comprehending complex (relative-clause) sentences and left IFG atrophy (Amici et al., 2007). A study by Peelle and colleagues on nonfluent PPA found relationships between impaired comprehension of complex sentences and cortical atrophy in left frontal regions (IFG, operculum, insula, dorsolateral frontal cortex), as well as the anterior STG (Peelle et al., 2008).

In addition to cortical regions, most current models of sentence comprehension also identify neural streams or *pathways*, that is, white matter tracts that connect cortical regions, including *dorsal* pathways (e.g., linking posterior temporal regions to inferior frontal regions via the parietal lobe, e.g., via the AF and superior longitudinal fasciculus [SLF]) and *ventral* pathways (e.g., linking posterior temporal cortex to the anterior temporal region via the temporal longitudinal fasciculus [TLF] and the inferior frontal cortex via the uncinate fasciculus [UF] and inferior frontal-occipital fasciculus [IFOF]) (Catani, Jones, & Ffytche, 2005). Both the dorsal and ventral pathways have been argued to play a role in sentence comprehension, but the specific functions of the two routes vary across models. Dorsal pathways, connecting posterior temporal to inferior frontal regions, via the AF, have been argued to support processing of complex syntactic structures (Friederici, 2012; Friederici & Gierhan, 2013) or syntactic processing in general (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hagoort & Indefrey, 2014). Because stroke-induced aphasia often is associated with marked disruption of white matter tracts, researchers have turned to PPA to examine the relation between tract integrity and language ability. In PPA, white matter tracts often are only partially compromised, allowing for such analyses. Indeed, associations between damage to dorsal routes (i.e., the AF and SLF) and impaired comprehension have been reported in PPA (Wilson et al., 2011). Catani and colleagues (2017) found that, while both dorsal and ventral routes were disrupted in a group of 30 patients with PPA, correlations between sentence comprehension as tested by the NAVS (Thompson, 2011) and the posterior segment of the AF were noted. Functional neuroimaging (see Heim & Specht, Chapter 4 in this volume) studies of sentence comprehension have also supported these findings. One study reported that listeners with PPA-G, in contrast with unimpaired adults, did not show greater activation in the left IFG when comprehending noncanonical versus canonical sentences (Wilson, Dronkers, et al., 2010; cf. Cooke et al., 2003). Another study found that syntactic comprehension impairments were associated with abnormal functional activation in left frontal regions (IFG, insula, ventral PCG) as well as posterior temporal (MTG, STG) and inferior and superior parietal regions (i.e., dysfunction of regions within the dorsal route) (Wilson et al., 2016).

In contrast, ventral language pathways connecting temporal to frontal regions have been argued on several models to support semantic processing (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hagoort & Indefrey, 2014) and appear to play little role in sentence-level deficits in PPA (Mandelli et al., 2014; Wilson, DeMarco, et al., 2014; Wilson et al., 2011). In the Catani et al. (2017) PPA study, ventral route (i.e., the UF and the TLF, but not the IFOF) disruptions were significantly correlated with single-word comprehension deficits. Some models, however, also propose a role for ventral pathways such as the

UF in basic syntactic comprehension and phrase-structure building (Friederici, 2012; Friederici & Gierhan, 2013), as well as comprehension in general (Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Hickok & Poeppel, 2015; Saur et al., 2008).

In contrast with sentence comprehension, relatively few studies have examined the neural correlates of impaired complex sentence production. In chronic agrammatism caused by stroke, we recently found that impaired sentence production (measured using the Sentence Production Priming Test of the NAVS) is associated with damage to the insula and inferior parietal regions (AG, SMG) (Lukic et al., 2014). Damage to the insula was specifically related to impairments in producing noncanonical (vs. canonical) sentences. Notably, Lukic et al. also found an association between lesions of the AF and sentence production. Turning to PPA, Rogalski and colleagues (Rogalski et al., 2011) used an anagram task to probe construction of complex sentences (the Northwestern Anagram Test [NAT]; Thompson, Weintraub, & Mesulam, 2012) and found that impaired performance was associated with atrophy in cortical regions including the anterior and posterior IFG, the ventral PCG and post-central gyrus, and the SMG. A study involving structured spoken sentence production found that impaired performance was associated with atrophy in the posterior IFG (DeLeon et al., 2012). In a study of narrative language production, atrophy in the IFG and surrounding frontal regions (e.g., the supplementary motor area [SMA]) was associated with reduced production of complex sentences with embedding, as well as a lower "syntactic composite" score (i.e., a principal component incorporating the rate of syntactic errors and the proportion of words occurring outside of sentences) (Wilson, Henry, et al., 2010). Further, dorsal language tracts have also been argued to play a particularly important role in language production (Hickok & Poeppel, 2015; Saur et al., 2008). Two studies found that damage to the AF/SLF was associated with impaired syntactic production (Mandelli et al., 2014; Wilson et al., 2011). One of these studies also implicated a second dorsal language pathway, connecting the left posterior IFG to the left SMA, in impaired sentence production, consistent with the claim that this pathway supports word sequencing (Mandelli et al., 2014). The role of this pathway in word sequencing may be specific to spoken-language production. Catani et al. (2013) examined the language functions of the left frontal aslant tract, which partially overlaps with the IFG-SMA pathway investigated by Mandelli et al. (2014). Catani and colleagues found that damage to the frontal aslant tract was associated with impaired fluency, but not with grammatical impairments. However, the grammatical production task used by Catani and colleagues was an anagram task (the Northwestern Anagram Test; Thompson, Weintraub, & Mesulam, 2012), which does not require spoken-language production. In contrast, the study by Mandelli and colleagues did require spoken-language production, and did find an association between the IFG-SMA pathway and grammatical abilities.

In summary, the preponderance of evidence suggests that damage to cortical regions, all within the dorsal language pathways, underlies both verb and sentence deficits in agrammatism. These regions include the left posterior STG, inferior parietal regions (AG, SMG), and inferior frontal regions (IFG). Additionally, sentence production engages the insula, SMA, and ventral PCG. The extant literature also shows that segments of the AF connect these regions, with the posterior segment associated with verb and sentence comprehension and anterior regions associated with verb and sentence production, whereas ventral language pathways play a relatively minor role.

CONCLUSION

In this chapter, we have provided an overview of research pertaining to verb- and sentence-processing deficits in agrammatism and their neural correlates. In future work, we expect that the study of agrammatism will become increasingly dynamic, with an emphasis on understanding change over time in language function and its neural substrates. To this end, a growing body of research has examined the neural correlates of aphasia recovery in the acute and subacute stages (e.g., Saur et al., 2006) as well as treatment-related recovery of sentence comprehension and production in chronic agrammatism (Thompson, den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010; Thompson, Riley, den Ouden, Meltzer-Asscher, & Lukic, 2013; Wierenga et al., 2006). Future work on recovery in stroke-induced agrammatism will likely also incorporate insights from theories of language (re)-learning in this population (Christiansen, Louise Kelly, Shillcock, & Greenfield, 2010; Goschke, Friederici, Kotz, & van Kampen, 2001; Schuchard, Nerantzini, & Thompson, 2017; Schuchard & Thompson, 2014, 2017; Zimmerer, Cowell, & Varley, 2014). A dynamic perspective is also necessary for understanding the mechanisms of language decline in agrammatic PPA, and how agrammatism can be effectively treated in the context of neurodegenerative disease (e.g., Hameister, Nickels, Abel, & Croot, 2017; Schneider, Thompson, & Luring, 1996).

In addition, developing a dynamic understanding of agrammatism will require integrating insights from studies using a wide range of methods (e.g., offline behavioral methods, eye-tracking, ERP, and neuroimaging measures of brain structure and function). In addition to the neuroimaging methods discussed here (i.e., structural measures of gray- and white-matter integrity, functional MRI), a fully specified model of agrammatism will also need to incorporate information about perfusion (cerebral blood flow; Thompson et al., 2010; Thompson et al., 2017) and functional and effective connectivity (e.g., den Ouden et al., 2012; Xiang, Fonteijn, Norris, & Hagoort, 2010). Thus, while much has already been accomplished in understanding the neurocognitive mechanisms of agrammatism, there is still much work to be done.

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CHAPTER 32

VERBAL WORKING MEMORY

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Introduction

In human verbal communication, there is often a period of time that intervenes between the sensory perception of a speech message and an appropriate response to that message. Consider the plight of the Starbucks *barista*: a fastidious customer comes to the front of the line and orders a complex expresso concoction. The cashier rings up the order and repeats it aloud: "grande double decaf almond praline soy latte with skim milk"—a verbal message containing all of 10 words and 15 syllables. The *barista*, meanwhile busy preparing a *tall lightly foamed caramel machiatto* for the previous customer, must mentally record and retain in memory the content of the new request. Although the spoken message describing an elaborate coffee drink has only a brief existence as a stream of acoustic vibrations in the physical world, it must nevertheless be transmitted and stably represented in the minds of three successive people. The customer *produces* the message, the cashier *repeats* the message, and the *barista* must *maintain* the message "in mind" until he or she has completed the order. When the drink arrives at the counter with a cheerful: "sir, your grande double decaf almond praline soy latte with skim milk is ready!" a bystander, uninitiated to this routine modern coffee-ordering spectacle, might be forgiven for considering the fulfillment of the customer's request to be something of a miracle. From the standpoint of the study of human cognition, the success of this commercial exchange depends critically not only on language competence—that is, the ability to perceive and produce speech—but also the ability to consciously hold on to a sequence of verbal information over a short period of time. In the terminology of cognitive psychology and neuroscience, we refer to this ability to retain information in an accessible state over brief periods of time as "working memory," a cognitive system that enables one to temporarily store and manipulate important pieces of information that are no longer readily available in the sensory environment.

In this chapter, I will first provide a historical overview of how working memory emerged as a concept in cognitive psychology. Next, I will describe the preeminent cognitive model of verbal working memory, the phonological loop, and how it explains critical laboratory phenomena associated with memory for verbal material. I will then discuss the attempts and associated difficulties in mapping and otherwise situating the phonological loop in the brain. Finally, I will cover the recent movement in the cognitive neuroscience of language to view verbal working memory as emerging from the language circuitry that underpins core language functions such as the perception and production on speech.

THE DEVELOPMENT OF THE CONCEPT OF SHORT-TERM MEMORY

Viewing memory as comprising two main compartments, one for the current contents of consciousness, and another for a more permanent record of experience, has gone in and out of fashion in the last century. William James (1890) coined the terms "primary memory" and "secondary memory" to refer to these two basic concepts, setting off a long-standing debate in the psychological sciences as to whether memory is a unitary faculty or whether it can be divided into different sub-components. In the mid-twentieth century most theorists viewed memory as a unitary system governed by a single set of principles that were largely invariant over time (Melton, 1963; Underwood, 1957). However, in the 1960s, cognitive psychology offered evidence for the existence of two memory systems, one for very recent events (short-term memory) and one for events that occurred in the more distant past (long-term memory).

A key piece of evidence supporting the "dual-store" view of memory came from studies of free recall. These studies showed that when subjects are presented with a list of words and must recall them in any order (free recall), performance is best for the first few items (the *primacy* effect) and for the last few items (the *recency* effect). When accuracy is plotted as a function of input order, it reveals a characteristic U-shaped pattern (Davelaar, Goshen-Gottstein, Ashkenazi, Haarmann, & Usher, 2005; Glanzer & Cunitz, 1966; Waugh & Norman, 1965), which is referred to as the *serial position curve*. However, if a short delay (e.g., 10 s) is placed between stimulus presentation and recall, during which subjects are required to engage in some distracting activity, the shape of the serial positive curve changed. Performance on early items (primacy) is relatively unaffected, but the recency effect is abolished (Glanzer & Cunitz, 1966; Postman & Phillips, 1965). Recency effects are attributed to a readout of the last few items in a list from short-term memory, and primacy effects reflect a long-term memory advantage for the first few items in a list due to the greater rehearsal devoted to those items. Moreover, recall from the long-term store requires a more effortful and slow probabilistic form of retrieval that depends more on associative, semantic, and contextual retrieval cues than does retrieval from the short-term store. However, the preceding interpretation of patterns of recency effects in immediate and delayed recall, as reflected in the operation of two stores, has long been disputed, and is complicated by the demonstration of recency effects that can span across minutes or even days (Bjork & Whitten, 1974; Crowder, 1982). One way to explain the existence of both short- and long-term recency effects is that they emerge from a common cause. Howard and Kahana (2002), for example, have argued that recency effects can be explained in terms of "temporal context," which is an internal process that continually evolves and drifts over time. During memory retrieval, this temporal context is reinstated, leading to recall of items that were temporally co-occurring. Both long- and short-term recency effects emerge because the temporal context at the offset of a memory list is most distinctive, and therefore most likely to be accessed. This leads to clustered recall of the most recent items of a list, and this phenomenon occurs over short and long scales and has nothing to do with the existence of short- and long-term memory stores. Although a more detailed discussion of this topic is beyond the scope of this chapter, it is important to keep in mind that whereas the bulk of cognitive neuroscience research assumes the existence of short- and long-term memory systems or stores, there are alternative and, indeed compelling, views that deny them any such existence (see also Davelaar et al. 2005; Sederberg et al. 2008; Lewandowsky et al., 2009).

In summary, short-term memory is a kind of limit of the online capacity of the brain's ability to hold and process information. Thus, short-term memory can be viewed as a cup into which sensory information flows. The capacity of the cup is fixed, and is prone to overflowing. The precise capacity of the cup varies across individuals (Unsworth & Engle, 2007), although as George Miller (1956) memorably pointed out, it tends to hover around a "magical number" of 7 plus or minus 2 (but see also Cowan, 2001). When incoming information exceeds the capacity of the cup, the spillover may yet still be recorded in a secondary container, that is, long-term memory.

NEUROLOGICAL DISSOCIATION OF SHORT- AND LONG-TERM MEMORY

One of the critical pieces of evidence supporting the existence of separable systems for short- and long-term memory was the discovery of patients with brain damage who appeared to have selective deficits affecting only long-term or only short-term memory. The most famous example of such a dissociation was the case of the patient H.M., whose medial temporal lobes were famously removed as a treatment of intractable epilepsy. The surgery resulted nearly complete loss in the ability to form new long-term declarative memories (Corkin, 2002; Scoville & Milner, 1957). H.M. and other patients with bilateral medial temporal lobe lesions that have subsequently been described (Squire, Stark, & Clark, 2004) live in a kind of "permanent present tense" (Corkin, 2013), unable to consciously recall events that occurred even a few minutes ago. Notwithstanding this severe impairment in the ability to form new long-term declarative memories, such patients appear to have little or no deficit on tests of short-term memory, such as repeating back short strings of digits (Baddeley & Warrington, 1970; Wickelgren, 1968), although deficits in short-term memory have been sometimes been observed in these patients in tests using novel visual objects (see Ranganath & Blumenfeld, 2005) or in tests of short-term associative memory (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Ryan & Cohen, 2004; Yee, Hannula, Tranel, & Cohen, 2014).

The neurobiological distinction between short-term and long-term memory was strongly supported by the discovery of patients with severely impaired short-term memory for numbers and words, together with a preserved ability to learn supra-span (e.g., greater than 10 items) word lists with repeated study (Baddeley, Papagno, & Vallar, 1988; Basso, Spinnler, Vallar, & Zanobio, 1982; Shallice & Warrington, 1970; Warrington & Shallice, 1969). Thus, in contrast to patient H.M., these patients were shown to be able to form new long-term (verbal) memories, and yet had little or no verbal short-term memory. Whereas H.M.'s memory deficit was a general memory impairment that applied to all forms of declarative information (e.g., verbal, visual, spatial), these particular "short-term memory patients," as they were to be called, had deficits confined to the auditory-verbal modality. The short-term memory deficits by these patients, in the purest cases (Shallice & Butterworth, 1977; Shallice & Vallar, 1990; Shallice & Warrington, 1977; Takayama, Kinomoto, & Nakamura, 2004; Vallar & Baddeley, 1984; Vallar, Di Betta, & Silveri, 1997), are not accompanied by severe deficits in language comprehension and production. Thus, patient J.B. (Shallice & Butterworth, 1977) was able to carry on conversations normally and to speak fluently without abnormal pauses, errors, or other aphasic symptoms. What this seemed to show was that verbal storage is not "built in" to the language-processing system, but is an independent entity in its own right, a memory buffer that exists not to support language per se, but rather as a passive "holding place" where recently encountered linguistic information can be temporarily stored. Thus, the discovery of "short-term memory patients" (Vallar, 2006) established a double dissociation both in brain localization (LTM: medial temporal lobe; verbal STM: temporoparietal cortex) and patterns of performance, between short- and long-term memory systems. In addition, the short-term memory disorder could be distinguished from severe disorders of language production and comprehension such as Broca's aphasia, Wernicke's aphasia, and other of the classic neurological language impairments.

WORKING MEMORY

The Working Memory model of Baddeley and colleagues (Baddeley, 1986, 2000, 2003; Baddeley & Hitch, 1974) was developed with an aim of explaining the relevant behavioral findings in the memory literature while also taking into account important neuropsychological case study reports, such as those reviewed in the preceding. In addition, whereas prior models of short-term memory tended to emphasize storage buffers as the receptacles for information arriving from the senses, Baddeley and Hitch (1974) focused on rehearsal processes, that is, strategic mechanisms for the maintenance of items in memory. Baddeley and Hitch (1974) attempted to account for a system that could simultaneously manipulate the current contents of memory and update information in working memory in the service of task goals. Such a system is especially important when one needs to maintain information over short periods in many complex cognitive activities, such as reading, mental calculation, spatial reasoning, and so forth.

Research has shown that in tests of serial recall, when subjects are prevented from engaging in subvocal rehearsal during a delay period that is inserted between stimulus presentation and recall, overall performance suffers (e.g., Baddeley, Thomson, & Buchanan, 1975). In the case of verbal material, this suggested that the ability to keep verbal sequences in working memory depends on covert articulatory processes. This insight was central to the development of the verbal component of working memory, the "phonological loop" (see later discussion), and led to a broader conceptualization of short-term memory that sought to explain not only how and why information enters and exits awareness, but also how resources are deployed in a strategic effort to capture and maintain the objects of memory in conscious awareness.

The major principles of the Working Memory model are that it is (1) a limited capacity system (i.e., there is only a finite amount of information directly available for processing in memory); (2) that specialized subsystems devoted to the representation of information of a particular type, for instance, verbal or visuospatial, are structurally independent of one another (i.e., the information represented in one domain is protected from the interfering effects of information that may be arriving to another domain); and, finally, (3) that storage of information in memory is distinct from the processes that underlie sensory perception; instead, there is a two-stage process whereby sensory information is first analyzed by perceptual modules and then transferred into specialized storage buffers that have no other role but to temporarily "hold" pre-processed units of information. Moreover, the pieces of information that reside in these specialized buffers are subject to passive, time-based decay as well as inter-item interference (e.g., similar-sounding words like "man, mad, map, cap, mad" can lead to interference within a specialized phonological storage structure); finally, the storage buffers have no built-in or internal mechanism for maintaining or otherwise refreshing their contents—rather, this must occur from without, through the process of rehearsal, which might be a motor or top-down control mechanism that can sequentially access and refresh the contents that remain active within the store.

The Working Memory model, first proposed by Baddeley and Hitch (1974) and later refined (Baddeley, 1986, 2000, 2003; Salame & Baddeley, 1982), argued for the existence of three functional components of working memory. The "central executive" was envisioned as a control system of limited attentional capacity, responsible for coordinating and controlling two subsidiary slave systems, a *phonological loop* and a *visuospatial sketchpad*. The phonological loop was responsible for the storage and maintenance of information in a verbal form, and the visuospatial sketchpad was dedicated to the storage and maintenance of visuospatial information. In the last decade, a fourth component, the "episodic buffer," has been added to the model in order to capture a number of phenomena related to interactions between short- and long-term memory that could not be readily explained within the original framework. In the following section, we will describe the phonological loop in more detail, as it is the central component underlying working memory for verbal material.

The Phonological Loop

As we have noted, the Working Memory model entails a separation of domain-specific mechanisms of memory maintenance and domain-general mechanisms of executive control (Figure 32.1). Thus, the verbal component of working memory, or the phonological loop, is regarded as a "slave" system that is under the supervisory control of the central executive component. Within the phonological loop, two interacting components—the phonological store and the articulatory rehearsal process—enable verbal representations to be maintained in an active state.

The phonological store is a passive buffer in which verbal information can be stored for brief (approximately 2-s) periods. The articulatory control process serves to refresh the contents of the store, thereby allowing the system to maintain sequences of verbal items in memory over some interval of time. This division of labor between two

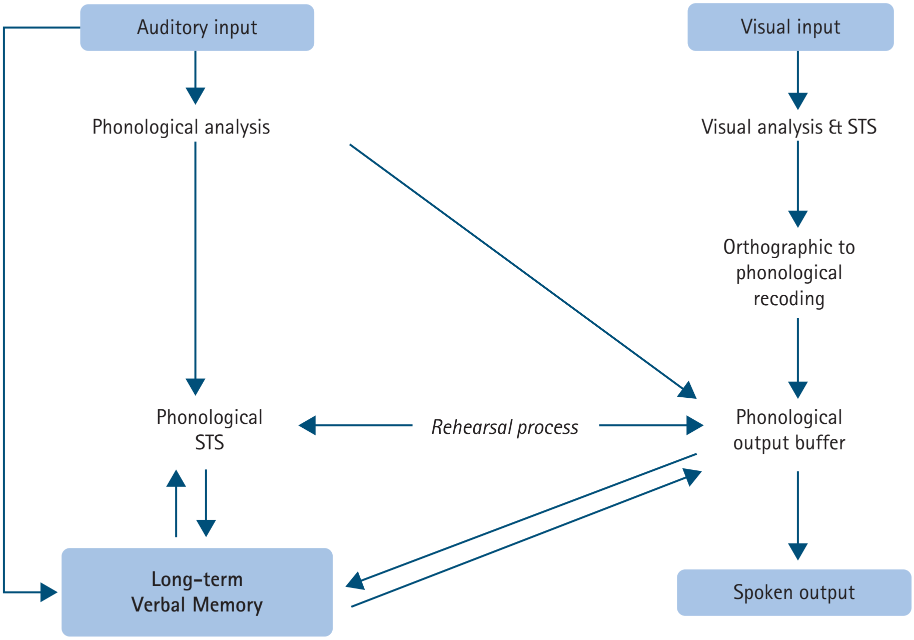

Auditory input
Visual input
Phonological analysis
Visual analysis & STS
Orthographic to phonological recoding
Phonological STS
Rehearsal process
Phonological output buffer
Long-term Verbal Memory
Spoken output

FIGURE 32.1. An anatomo-functional model of phonological short-term memory.

Abbreviation: STS = superior temporal sulcus.

Source: Based on Vallar et al. (1997), and Baddeley, Gathercole, and Papagno (1998).

interlocking components, one an active *process* and the other a *passive* store, is crucial to the model's explanatory power. For instance, when the articulatory control process is interfered with through the method of articulatory suppression (e.g., by requiring subjects to say "hiya" over and over again), items in the store rapidly decay, and recall performance suffers greatly. The phonological store, then, lacks a mechanism of reactivating its own contents but possesses memory capacity, whereas the articulatory rehearsal process lacks an intrinsic memory capacity of its own, but can exert its effect indirectly by refreshing the contents of the store.

The phonological loop model of verbal working memory has stood the test of time largely because it explains many of the behavioral phenomena associated with verbal memory performance in a simple and intuitive way. It is important to briefly note what these core behavioral phenomena are, and how the phonological loop model accounts for them. The appeal of the model comes partly from its parsimony—with only a very minimal set of functional specifications, it is able to account for a large number of behavioral findings. It therefore provides a benchmark that any competing model, whether neural or purely cognitive, must be able to match. In the paragraphs that follow, I will give an overview of how the phonological loop explains certain well-established behavioral phenomena associated with verbal working memory, namely, the *phonological similarity effect*, the *word-length effect*, the effect of *articulatory suppression*, and the *irrelevant sound effect* (Repovs & Baddeley, 2006). The phonological similarity effect refers to the finding that similar sounding sets of words are more difficult to retain in memory than sets of phonologically dissimilar words (Conrad & Hull, 1964). The locus of this effect is the phonological store, and it results from the increased amount of interference that occurs between memory traces that share overlapping representational (e.g., phonemic) features, relative to those that do not.

The word-length effect simply refers to the fact that lists of words that take more time to articulate—longer words—are more poorly remembered than words that take less time to articulate (Baddeley et al., 1975; Mueller, Seymour, Kieras, & Meyer, 2003). This occurs not only between sets of words that have different numbers of syllables, but also for sets of words that are equated for number of syllables but are, nevertheless, unequal in absolute articulatory duration. The effect is explained by assuming that items in the phonological store suffer time-based decay that can only be reversed by way of articulation. Thus, as the articulatory loop cycles through a set of long words, the overall time elapsed between successive iterations will be greater, and, therefore, the probability that one of the several items in the store may have (irretrievably) decayed will be consequently increased. This effect, then, is jointly determined by the properties of the rehearsal process (rate of articulation) and that of the phonological store (rate of decay).

The negative effect of articulatory suppression on recall performance is observed when subjects are prevented from using inner speech either during presentation or during a delay inserted before recall. Thus, as articulatory suppression interferes with the articulatory rehearsal process, the mechanism that is ordinarily used to refresh the items in the phonological store, the system is therefore unable to counteract trace decay, thus leading to a decline in recall performance.

The irrelevant sound effect occurs when the to-be-remembered verbal stimuli are accompanied by a stream of unattended auditory information (Macken, Mosdell, & Jones, 1999; Salame & Baddeley, 1982; Tremblay, Nicholls, Alford, & Jones, 2000). These "irrelevant sounds" need not be in the speaker's native language or even phonemic to be disruptive, provided there is some degree of variation in the sound stream. For instance, a single tone or even white noise does not have an effect, although a changing sequence of tones does cause impairment (Jones, Madden, & Miles, 1992). The locus of the irrelevant sound effect is in the phonological store, where the incoming acoustic information interferes with the to-be-remembered items in the store. Because the presentation of irrelevant visual-verbal information does not have an effect on recall, it is assumed that auditory information has obligatory access to the store, whereas visual-verbal information does not. How, then, does visual-verbal information enter the phonological store? The answer, supported by several lines of evidence (Baddeley, Lewis, & Vallar, 1984; Levy, 1971), is that textual information must first be recoded phonologically before it can enter the store. This recoding process, moreover, requires the involvement of the articulatory rehearsal process, as subvocalization is necessary to reroute visually derived verbal information into the phonological store. In support of this contention is the finding that articulatory suppression abolishes the phonological similarity effect for visual, but not auditory, presentation. Because auditory information has obligatory access to the store, articulatory suppression has no effect on its deposition within the store. For visual presentation, however, articulatory suppression ties up the rehearsal system, preventing phonological recoding of visual-verbal material and, consequently, blocking subvocally mediated access to the store. In the preceding sections, we briefly outlined the main components of the phonological loop, as well as the manner in which its architecture and functional characteristics account for certain reliable effects observed in studies of verbal short-term memory. We should make clear that it is not universally accepted that every detail of the phonological loop is perfectly supported by available evidence. For instance, there is a great deal of debate about whether the word-length effect is actually caused by an increase in the absolute spoken duration of the items, or whether it is better explained by, for instance, the phonological complexity of the items (Caplan, Rochon, & Waters, 1992; Mueller et al., 2003).

In summary, the Working Memory memory model of Baddeley and colleagues describes a system for the maintenance and manipulation of information that is stored in domain-specific memory buffers. Separate cognitive components are dedicated to the functions of storage, rehearsal, and executive control. Informational encapsulation and domain segregation dictates that auditory-verbal information and visual information are kept in separate storage subsystems—the phonological loop and the visuospatial sketchpad, respectively. These storage subsystems themselves comprise specialized components for the passive storage of memory traces, which are subject to time and interference-based decay, and for the reactivation of these memory traces by way of simulation, or rehearsal. Thus, storage components represent memory traces, but have no internal means of refreshing them, whereas rehearsal processes (e.g., articulatory) have no mnemonic capacity of their own, but can reactivate the decaying traces held in temporary stores. In the next sections, we will examine how neuroscience has built on the cognitive foundation of the Working Memory model of Baddeley and colleagues to refine our understanding of how information is maintained and manipulated in the brain. We will see that in some cases, neuroscientific evidence has bolstered and reinforced aspects of the Working Memory model, whereas in other cases neuroscience has compelled a departure from certain core principles of the Baddeleyan concept.

The Neuroscientific Basis of Verbal Working Memory

Research on the neural basis of verbal working memory has some unique challenges and is in several ways more difficult to study than, for example, visual or spatial working memory. For example, whereas in visual working memory many of the most influential ideas and concepts have derived from work in nonhuman primates and other animals, verbal working memory is a uniquely human phenomenon, and has therefore benefited from animal research only in terms of broad neuroscience principles.

Even research on the primary modality relevant to verbal working memory, that of audition, is surprisingly scarce in the monkey literature, owing to the difficulty in training nonhuman primates to perform delayed response tasks with auditory stimuli, which can take upward of 15,000 learning trials (Fritz, Mishkin, & Saunders, 2005). Because of the lack of animal work on verbal working memory, neuroscience has often looked to cognitive psychological models, such as the Working Memory model of Baddeley and colleagues, for a sensible framework for interpreting neuroscientific evidence about verbal working memory. Of course, many of the classic neurological studies of language were carried out before “working memory” existed as a concept, let alone as an object of avid neuroscience inquiry. Nevertheless, the core idea of Baddeley and colleagues’ phonological loop—namely, that verbal information can be reciprocally transferred between auditory and motor components—has a clear cognate in the Wernicke-Lichtehim-Geschwind model of language organization, the core of which originated in Carl Wernicke’s 1874 monograph on the aphasias (Geschwind, 1965b; Wernicke, 1874; see, in this volume, Blumstein, Chapter 1, and Wilson, Chapter 2). A fundamental challenge to the cognitive neuroscience of verbal working memory has been to integrate both empirical data and theoretical constructs that have emerged from different subfields—cognitive, neurological, neuropsychological—of inquiry in the brain and behavioral sciences.

NEUROLOGICAL STUDIES OF LANGUAGE AND VERBAL SHORT-TERM MEMORY

Early neurological investigations of patients with language disturbances, or aphasia, revealed that lesions to specific parts of the cerebral cortex could cause selective deficits in language abilities (Goodglass, 1993). Thus, lesions to the inferior frontal gyrus and surrounding cortex are associated with Broca's aphasia, a disorder that causes severe impairments in speech production. Broca's aphasia is not, however, a disorder of peripheral motor coordination, such as the ability to move and control the tongue and mouth, but rather is a disorder of the ability to plan, program, and access the motor codes required for the production of speech (Goodglass, 1993; Mohr et al., 1978). Lesions to the posterior superior temporal gyrus (STG) and surrounding cortex, on the other hand, are associated with Wernicke's aphasia, a complex syndrome that is characterized by fluent but error-filled production, and poor comprehension and perception of speech. A third, less common syndrome, called conduction aphasia, typically caused by lesions in the auditory cortex and posterior Sylvian region (generally less extensive and relatively superior to lesions causing Wernicke's aphasia), is associated with relatively preserved speech perception and comprehension, occasional errors in otherwise fluent spontaneous speech (e.g., phoneme substitutions), and severe difficulties with verbatim repetition of words and sentences (Axer, 2001; Baldo & Dronkers, 2006; H. Damasio & Damasio, 1980).

From the standpoint of verbal short-term memory, there are a number of important points to be drawn from these three classic aphasic syndromes. First, the neural structures that underlie the perception and production of speech are partly dissociable (see, in this volume, Tremblay, Deschamps, & Dick, Chapter 15, and Hickok, Chapter 20). While it is tempting to postulate that posterior temporal lesions primarily affect receptive language functions and anterior lesions affect productive language functions, this is not quite true: both Wernicke's aphasia and conduction aphasia are caused by posterior lesions, yet only the former is associated with a major receptive language disturbance, while both syndromes involve a deficit in speech production. Moreover, lesions in and around the inferior frontal gyrus (Broca's area), although normally associated with deficits in speech production (labored, nonfluent speech), can also lead to deficits in the comprehension of grammatically complex sentences and subtle deficits in speech perception (Berndt, Mitchum, & Wayland, 1997; Caplan, Baker, & Dehaut, 1985; see Thompson & Mack, Chapter 31 in this volume). Second, the previously mentioned disorders affect basic aspects of language processing, such as the comprehension, production, and perception of speech. Third, the classical Wernicke-Lichteim-Geschwind (Geschwind, 1965a) model of language explains each of these three syndromes as disruptions to components of a neuroanatomical network of areas, in the inferior frontal and superior temporal cortices, that subserve language function. Finally, it should not be surprising that aphasic syndromes associated with poor language performance have also been shown to affect verbal working memory (Burgio & Basso, 1997; De Renzi & Nichelli, 1975). This cannot be taken to necessarily imply that verbal working memory is a function of the core language network. For example, as we have noted earlier, input to the storage component of the phonological loop theoretically depends on a functioning language system, while not itself participating in core language processes such as speech perception and speech production. Thus, the association between language disturbances and verbal working memory impairment does not prove that the two systems are functionally equivalent.

This is especially true in light of evidence from neuropsychology, discussed earlier, showing that verbal short-term memory impairment need not accompany a basic impairment to the language faculty. An interpretation consistent with the phonological loop model of verbal working memory is that a selective deficit to verbal short-term memory is caused by lesions that have damaged the phonological store while leaving language perception and production centers intact. Moreover, these patients offer credence to the conceptualization of memory, exemplified by the phonological loop, as a distinct entity in its own right, whose functional purpose is to store and maintain information in mind, rather than to analyze and process incoming sensory input. Although the evidence for such a functional dissociation on the basis of these "short-term memory patients" is intriguing and compelling, the anatomical localization of these lesions, as we shall see, presents cognitive neuroscience with a difficult puzzle.

With respect to the "short-term memory patient" discussed earlier, one must ask how a lesion in the middle of the perisylvian speech center encompassing the temporoparietal area could produce such a pure short-term memory deficit without any collateral impairment in basic online language functioning. One possibility is that the precise location of the brain injury is critical, so that a particularly focal and well-placed lesion in temporoparietal cortex might spare cortex critical for speech perception and speech production, while damaging a region dedicated to the temporary storage of auditory-verbal information. Indeed, this is exactly what would be predicted if the "phonological store" component of Baddeley's Working Memory model were to be specifically damaged.

The number of patients that have been described with a selective impairment to auditory-verbal short-term memory is small, however, and the lesion locations that have been reported are not clearly distinguishable from those that might, in another patient, have led to conduction or Wernicke's aphasia (Baldo & Dronkers, 2006; Damasio, 1992; Goodglass, 1993). One way that has been used to address this puzzle is to use functional neuroimaging to investigate the extent to which the brain regions supporting general language processing (perception and production of speech) are dissociable from regions that are recruited during verbal short-term memory.

Functional Neuroimaging Studies of Verbal Working Memory

The first study that attempted to localize the components of phonological loop in the brain was that of Paulesu and colleagues (1993). In one task, English letters were visually presented on a monitor and subjects were asked to remember them. In a second task, letters were presented and rhyming judgments were made about them (press a button if letter rhymes with "B"). In a baseline condition, Korean letters were visually presented and subjects were asked to remember them using a visual code. According to the authors' logic, the first task would require the contribution of all the components of the phonological loop—subvocal rehearsal, phonological storage, and executive processes—while the second (rhyming) task would only require subvocal rehearsal and executive processes. This reasoning was based on previous research showing that when letters are presented visually (Vallar & Baddeley, 1984), rhyming decisions engage the subvocal rehearsal system, but not the phonological store. Thus, a subtraction of the rhyming condition from the letter-rehearsal condition should isolate the neural locus of the phonological store. First, results were presented for the two tasks requiring phonological processing with the baseline tasks (viewing Korean letters) that did not. Several areas were shown to be significantly more active in the "phonological" tasks, including (in all cases, bilaterally): Broca's area (BA 44/45), the supplementary motor cortex (SMA), the insula, the cerebellum, Brodmann area 22/42, and Brodmann area 40. Subtracting the rhyming condition from the phonological short-term memory condition left a single brain area: Brodmann area 40—the neural correlate of the phonological store.

The articulatory rehearsal process recruited a distributed neural circuit that included the inferior frontal gyrus, cerebellum, supplementarty motor area, and premotor cortex. Activation of multiple brain regions during articulatory rehearsal is not surprising, given the complexity of the process and the variety of lesion sites associated with a speech production deficit. On the other hand, the localization of the phonological store in a single brain region, BA 40 (or the supramarginal gyrus of the parietal lobe), fits well with the idea of a "receptacle" where phonological information is temporarily stored. A number of follow-up positron emission tomography (PET) studies, using various tasks and design logic, generally replicated the basic finding of the Paulesu et al. (1993) study, namely, a fronto-insular-cerebellar network associated with rehearsal processes, and a parietal locus for the phonological store (Awh et al., 1996; Jonides et al., 1998; Salmon et al., 1996; Schumacher et al., 1996; Smith & Jonides, 1999). In short, early PET studies of verbal working memory were interpreted as broadly supporting the architecture of the phonological loop, with storage being subserved by a left parietal lobe structure outside the core language network, and articulatory rehearsal associated with regions known to be involved in motor speech planning.

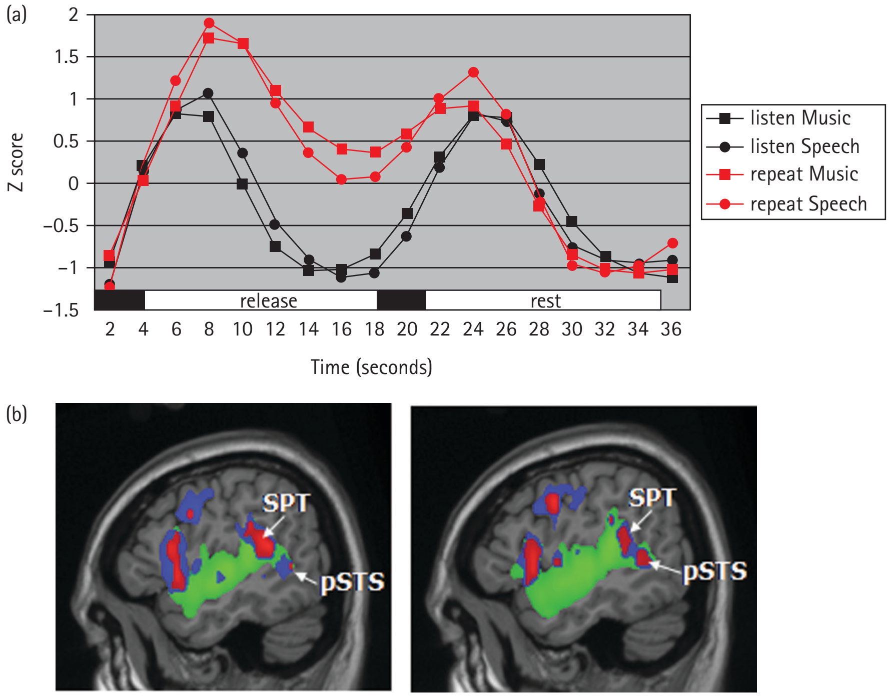
Becker et al. (1999), however, questioned whether the localization of the phonological store in the left parietal cortex could be reconciled with the logical architecture of the phonological loop. For instance, as reviewed earlier, a key element of the phonological loop model is that auditory information (whether it be speech, tones, music, or white noise), but not visual information, has *obligatory access* the phonological store. The reason for this difference is to account for dissociations in memory performance that depend on the modality in which information is presented. For instance, the presentation of distracting auditory information while subjects attempt to retain a list of verbal items in memory impairs performance on tests of recall. In contrast, the presentation of distracting visual information during verbal memory retention has no impact on verbal recall. This phenomenon—the irrelevant sound effect—is explained by assuming that auditory information always enters the phonological store, but that visual-verbal information only enters the store when it is explicitly subvocalized. Becker et al., however, argued that if indeed auditory information has automatic access to the phonological store, its "neural correlate" should be active even during *passive auditory perception*. Functional neuroimaging studies of passive auditory listening (e.g., with no memory component), however, do not show activity in the parietal region that had been associated in previous studies with phonological storage, but rather show activation that is largely confined to the superior temporal lobe (e.g., Binder et al., 2000).

A second difficulty with a parietal locus of the phonological store is that efforts to show verbal mnemonic specificity to maintenance-related activity in the parietal lobe have not been successful (Chein, Ravizza, & Fiez, 2003). Instead, it has been shown that working memory for words, visual objects, and spatial locations all activate the area (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005; Niendam et al., 2012; Nystrom et al., 2000; Zurowski et al., 2002). Thus, if there were a perfect "neural correlate" of the phonological store, it must reside within the confines of the auditory cortical zone of the superior temporal cortex.

Event-Related fMRI Studies of Verbal and Auditory Working Memory

Studies using event-related fMRI (see Heim & Specht, Chapter 4 in this volume), with its ability to isolate delay-period activity during working memory, have greatly improved our understanding of the neural circuitry associated with verbal working memory maintenance. Postle et al. (1999) showed, with visual-verbal presentation of letter stimuli, that delay-period activity in single subjects was often localized in the posterior superior temporal cortex, rather than the parietal lobe that was typically identified in the early PET studies reviewed earlier. Buchsbaum et al. (2001) also used an event-related fMRI paradigm, in which, on each trial, subjects were presented with acoustic speech information that they then rehearsed subvocally for 27 seconds, followed by a rest period. Analysis focused on identifying regions that were responsive *both* during the perceptual phase and the rehearsal phase of the trial. Activation occurred in two regions in the posterior superior temporal cortex, one in the posterior superior temporal sulcus (STS) bilaterally, and one along the dorsal surface of the left posterior planum temporale, that is, in the Sylvian fissure at the parietal-temporal boundary (area Spt). Notably, while the parietal lobe did show delay-period activity, it was unresponsive during auditory stimulus presentation. In a follow-up study, Hickok et al. (2003) showed that the same superior temporal regions (posterior STS and Spt) were active both during the perception and delay-period maintenance of short (5 s) musical melodies, suggesting that these posterior temporal storage sites are not restricted to speech-based, or "phonological," information (Figure 32.2).

Several subsequent studies have confirmed the role of Spt in internal rehearsal of musical and speech sequences (Hashimoto, Lee, Preus, McCarley, & Wible, 2010; Hickok, Okada, & Serences, 2009; Koelsch et al., 2009; see Ogg & Slevc, Chapter 35 in this volume). Acheson et al. (2011) used fMRI to identify posterior temporal regions activated during verbal working memory maintenance, and then used repetitive transcranial magnetic stimulation (TMS) to these sites while subjects performed a rapid-paced reading task that involved language production but no memory load. TMS (see Schuhmann, Chapter 5 in this volume) applied to the posterior temporal area



maintain music

maintain speech

FIGURE 32.2. Main results from Hickok et al. (2003) study of verbal and musical working memory maintenance. (A) Averaged time course of activation over the course of a trial in area Spt for speech and music conditions. Timeline at bottom shows structure of each trial; black bars indicate auditory stimulus presentation. Red traces indicate activation during rehearsal trials, black traces indicate activity during listen-only trials in which subjects did not rehearse stimuli at all. (B) Activation maps of in the left hemisphere (sagittal slices) showing three response patterns for both music rehearsal (left) and speech rehearsal trials (right): auditory-only responses shown in green; delay-period responses shown in blue; and auditory + rehearsal responses shown in red. Arrows indicate the location of area Spt.

Source: Reproduced from Hickok et al. (2003).

significantly interfered with paced reading, arguing for common neural substrate for language production and verbal working memory. Fegen et al. (2015) has shown that area Spt, the dorsal premotor cortex, and the inferior frontal gyrus are modulated by both the rate of covert rehearsal (number of items rehearsed per second) and the overall memory load (total number of items to retain in memory). However, regions associated with "domain-general" cognitive control processing, the dorsolateral prefrontal cortex (PFC) and posterior parietal cortex, are only modulated by memory load. This finding reinforces the notion that verbal working memory maintenance is a distributed operation that depends on the cooperation of multiple networks to store and maintain phonological information over time.

Stevens (2004) and Rama et al. (2004) have shown that memory for voice identity, independent of phonological content (i.e., matching speaker identity as opposed to word identity), selectively activates the mid-STS and the anterior STG of the superior temporal region, but not the more posterior and dorsally situated Spt region. Buchsbaum et al. (2005) have further shown that the mid-STS is more active when subjects recall verbal information that is acoustically presented than when the information is visually presented, whereas area Spt shows equally strong delay-period activity for both auditory and visual forms of input (see also Hashimoto et al., 2010). This finding is supported by regional analyses of structural MRI in large groups of patients with brain lesions that have showed that damage to the STG is most predictive of auditory short-term memory impairment (Koenigs et al., 2011; Leff et al., 2009). Leung et al. (2011) have also shown a dissociation between auditory object and spatial working memory, with the former activating more ventral stream auditory areas and the latter activating the dorsal parietal lobe. Thus, it appears that different regions in the temporoparietal area are attuned to different qualities or features of a verbal stimulus, such as voice information, input modality, phonological content, spatial location, and lexical status (e.g., Martin & Freedman, 2001)—and all of these codes may play a role in the short-term maintenance of verbal information.

Additional support for a feature-based topography of auditory association cortex comes from neuroanatomical tract-tracing studies in both monkeys and humans that have revealed separate temporo-prefrontal pathways arising along the anterior-posterior axis of the superior temporal region (Bavelier et al., 1998; Rauschecker, 2011; Romanski, 2004; Romanski et al., 1999; Saur, Kreher, & Schnell, 2008). The posterior part of the STG projects to dorsolateral PFC (BA 46, 8), whereas neurons in the anterior STG are more strongly connected to the ventral PFC, including BA 12 and 47. Several authors have suggested, similar to the visual system, a dichotomy between ventral-going auditory-object and dorsal-going auditory-spatial processing streams (Arnott, Binns, Grady, & Alain, 2004; Rauschecker & Tian, 2000; Tian, Reser, Durham, Kustov, & Rauschecker, 2001). Thus, studies have shown that the neurons in the rostral STG show more selective responses to classes of complex sounds, such as vocalizations, whereas more caudally located regions show more spatial selectivity (Chevillet, Riesenhuber, & Rauschecker, 2011; Rauschecker & Tian, 2000; Tian et al., 2001).

Hickok and Poeppel (2007) have proposed that human speech processing also proceeds along diverging auditory dorsal and ventral streams, although they emphasize the distinction between perception for action, or auditory-motor integration, in the dorsal stream and perception for comprehension in the ventral stream (see Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume). Buchsbaum et al. (2005) have shown with fMRI time series data that, consistent with the monkey connectivity patterns, the most posterior and dorsal part of the superior temporal cortex, area Spt, shows the strongest functional connectivity with dorsolateral and posterior (premotor) parts of the PFC, while the mid-portion of the STS is most tightly coupled with BA 12 and 47 of the ventrolateral PFC (see Figure 32.3). Moreover, gross distinctions between anterior (BA 47) and posterior (BA 44/6) parts of the PFC have been associated with conceptual-semantic and phonological-articulatory aspects of verbal processing (Poldrack et al., 1999; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). fMRI studies have also shown that maintenance of verbal-semantic information relies to a greater extent on the anteroventral aspects of the temproal lobe than does mainteance of phonological information (e.g., nonword sequences) (Fiebach, Rissman, & D'Esposito, 2006; Shivde & Thompson-Schill, 2004).

Taken together, findings from functional neuroimaging have shown that the maintenance of verbal information in working memory relies on a distributed network of primarily frontal, temporal, and parietal brain regions. The particular topography of activation depends on the content matter of the to-be-remembered stimuli and/or current task goals. Moreover, activation patterns during memory for musical or tonal sequences overlaps considerably with that for phonological sequences. There does not appear to be

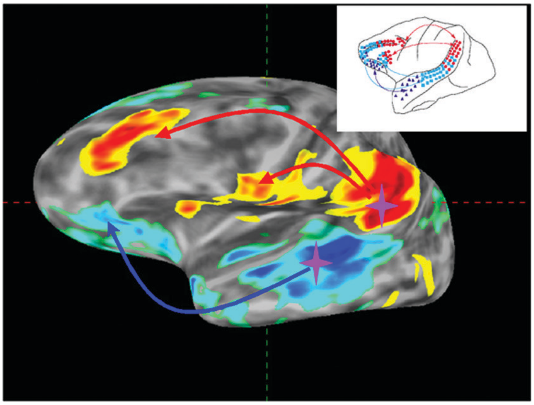


FIGURE 32.3. Map of functional connectivity delay period maintenance of verbal stimuli from Buchsbaum et al. (2005). Seed regions for correlation analysis are denoted by stars located in area Spt and the middle part of the STS. Warm colors show areas more strongly correlated with Spt than with STS; Cold colors show areas more strongly correlated with STS than Spt. Inset shows temporal-prefrontal connectivity in the monkey.

Abbreviation: STS = superior temporal sulcus.

Source: Inset reproduced from Romanski et al. (2001).

a single brain region where verbal information is passively stored, as would be predicted by the phonological loop model. Rather, it seems that short-term mnemonic storage is embedded in the very neural structures that support the auditory-verbal perception and production, and that these areas comprise a distributed fronto-temporo-parietal network.

Reconciling Neuropsychological and Functional Neuroimaging Data

Earlier we posed the question as to how a lesion in posterior Sylvian cortex, an area of known importance for online language processing, could occasionally produce an impairment restricted to phonological short-term memory. One solution to this puzzle is that subjects with selective verbal short-term memory deficits from temporoparietal lesions retain their perceptual and comprehension abilities due to the sparing of the ventral stream pathways in the lateral temporal cortex, whereas the preservation of speech production is due to an unusual capacity in these subjects for right-hemisphere control of speech (Buchsbaum & D'Esposito, 2008; Hickok & Poeppel, 2004; Nadeau, 2001). The short-term memory deficit arises, then, from a selective deficit in auditory-motor integration—or the ability to translate between acoustic and articulatory speech codes—a function that is especially taxed during tests of repetition and short-term memory (Buchsbaum & D'Esposito, 2008). Conduction aphasia, the aphasic syndrome most often associated with a deficit in auditory repetition and verbal short-term memory in the absence of any difficulty with speech perception, may reflect a disorder of auditory-motor integration (see Hickok, Chapter 20 in this volume). Indeed, it has recently been shown that the lesion site most often implicated in conduction aphasia circumscribes area Spt in the posteriormost portion of the superior temporal lobe, a link between a disorder of verbal repetition and a region in the brain often implicated in tasks of verbal working memory (Buchsbaum, Baldo, Okada, & Berman, 2011; see Figure 32.4). Thus, impairment in the ability to temporarily store verbal information, as occurs in conduction aphasia, may result from damage to a system, area Spt, which is critical for the interfacing of auditory and motor representations of sound.

Summary and Conclusions

Elucidation of the cognitive and neural architectures underlying verbal working memory has been an important focus of neuroscience research for much of the past two decades. The emergence of the concept of working memory, with its emphasis on the utilization of the information stored in memory in the service of behavioral goals, has

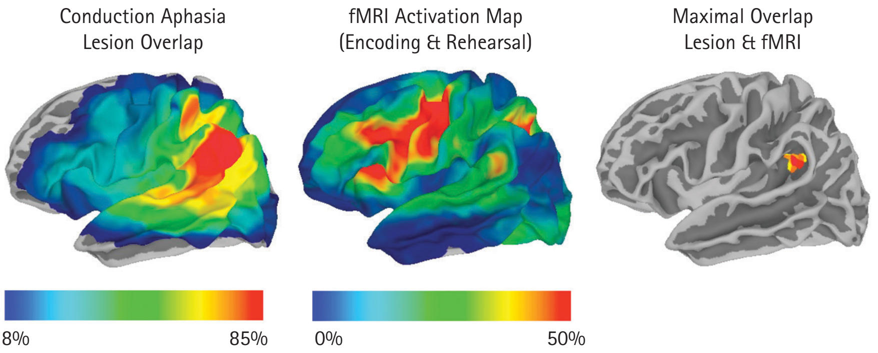


FIGURE 32.4. A comparison of conduction aphasia, phonological working memory in fMRI, and their overlap. The leftmost panel surface shows the regional distribution lesion overlap in patients with conduction aphasia (max is 12/14, or 85% overlap). Middle panel shows the percentage of subjects showing maintenance-related activity in a phonological working memory task. The right panel shows the area of maximal overlap between the lesion and fMRI surfaces (lesion > 85% overlap and significant fMRI activity for conjunction of encoding and rehearsal).

Source: Reproduced from Buchsbaum et al. (2011).

enlarged our understanding and broadened the scope of neuroscience research of short-term memory. Data from numerous studies have been reviewed and have demonstrated that a network of brain regions, principally in the temporal and frontal lobes, is critical for the active maintenance of internal verbal representations. It is clear from these investigations that verbal memory cannot be localized to a single brain region, but is rather an emergent property of the functional interactions between the frontal and posterior neocortical regions. Numerous questions remain about the neural basis of this complex cognitive system, but studies such as those reviewed in this chapter should continue to provide converging evidence that may provide answers to the many residual questions.

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CHAPTER 33

SUBCORTICAL CONTRIBUTIONS TO LANGUAGE

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Historical Perspective

Kinnier Wilson's (1925) depiction of the basal ganglia (BG) as the dark basements of the brain is still somewhat true when considering our understanding of the relationship between the subcortex and human language function. A range of possible functional attributes of these structures have been proposed based on studies of individuals with various subcortical pathologies, surgical lesions and electrical stimulation during neurosurgical procedures, and more recently through functional neuroimaging studies. This effort has elucidated motor and possible higher level/cognitive functions that the BG and thalamus may contribute to, yet the question of whether these deep structures play a critical role in language function remains a point of contention.

The first avenue for investigating this question empirically has been through clinico-anatomical studies of language function in individuals with vascular lesions involving the dominant BG (see also Wilson, Chapter 2 in this volume). Yet since the observation by Marie (1906) and Moutier (1908) (as cited in Wallesch & Papagno, 1988) early last century that subcortical lesions may be associated with language deficits, and a subsequent wealth of subcortical investigations in the past 50 years, the understanding of language function in this population has remained unclear, and advances in the theoretical conception of BG language function have been largely piecemeal. Although several theories of subcortical language function were postulated (e.g., Crosson, 1992; Wallesch & Papagno, 1988) and revised (Crosson, 1999), this field of inquiry did not progress for many years, unlike the revision of classical aphasia subtypes and impairments, which was further specified in terms of underlying processing components (Blumstein, 1997; see also Blumstein, Chapter 1 in this volume) and more recently has been incorporated into dominant models such as the dual-stream model (see Hickok, Chapter 20 in this volume).

One plausible explanation for this disparity, which has gained increased currency, is the notion that the BG play no direct role in language function, but that any language deficits which are associated with vascular BG lesions arise from cortical dysfunction (Nadeau & Crosson, 1997). Nadeau and Crosson (1997) provide comprehensive evidence for the lack of a coherent pattern or syndrome of language impairment following BG lesions, although it should be noted that this observation is based on traditional language measures sensitive to classical aphasia symptoms, allowing for the possibility that other functions may still be consistently impaired following subcortical lesions. Furthermore, observations of classical syndromes in aphasia following cortical lesions have also been criticized on the basis of significant heterogeneity within supposed syndromes in terms of both language presentation and lesion location. Regardless, the argument that aphasia subsequent to BG lesions was due in particular to cortical hypoperfusion was subsequently supported in a compelling fashion by the findings of Hillis et al. (2002), who observed a strong relationship between the presence of aphasia and the presence of cortical hypoperfusion after subcortical strokes, such that aphasic symptoms were only observed in the presence of cortical hypoperfusion. Critically, such hypoperfusion is not detected with structural imaging. This does not preclude the possibility that the BG may still contribute to language functions, but lends credence to the notion that any role is likely to be indirect or supportive. It should also be noted that the preceding observation that language impairments following BG strokes were predominantly due to cortical hypoperfusion does not appear to extend to thalamic strokes, where Sebastian et al. (2014) recently demonstrated the presence of aphasia following thalamic lesions without evidence of cortical hypoperfusion. Nadeau and Crosson (1997) also provide clear evidence of lexical-semantic impairments following thalamic strokes, which will be described further in the following.

Recent Advances in Understanding Relevant Subcortical Circuitry

When examining possible subcortical contributions to language, it is important to consider the important position of subcortical components in relation to various cortical regions that have been implicated in language or language-relevant processing. Indeed, the potential role of subcortical structures in language has been largely conceptualized in terms of subcortical-cortical circuitry (Crosson, 1992; Wallesch & Papagno, 1988). The striatum was originally considered a funnel that integrates information received from diverse cortical regions; however, this notion was largely superseded by the common view of the striatum as a "multi-laned throughway" that forms part of multiple segregated circuits connecting the cortex, the BG, and the thalamus (Alexander, Delong, & Strick, 1986; Middleton & Strick, 2000). Five anatomically segregated and possibly functionally distinct circuits are well established (see Middleton & Strick, 2000, for a review) (see Figure 33.1). These subcortical-cortical systems follow the basic route of cortex-striatum-globus pallidus/substantia nigra-thalamus-cortex in a unidirectional fashion. Each frontal-subcortical circuit contains a direct pathway between the striatum and the globus pallidus interna/substantia nigra complex, and an indirect pathway from the striatum to the globus pallidus interna/substantia nigra via the globus pallidus externa and subthalamic nucleus (STN). In addition, the STN is involved in a hyperdirect pathway receiving inputs from the frontal cortex and directly projecting to the globus pallidum. Each circuit includes an open and closed component.

Of these five circuits, Figure 33.1 illustrates the circuits with cortical components relevant to language (dorsolateral prefrontal cortex, anterior cingulate, orbitofrontal), but it should be noted that these regions are associated with domain-general cognitive processing (including executive function, cognitive control), rather than language-specific functions per se (see Tremblay, Deschamps, & Dick, Chapter 15 in this volume). Crosson et al. (2003) provided functional magnetic resonance imaging (fMRI) (see Heim & Specht, Chapter 4 in this volume) evidence suggesting the possibility of a modified

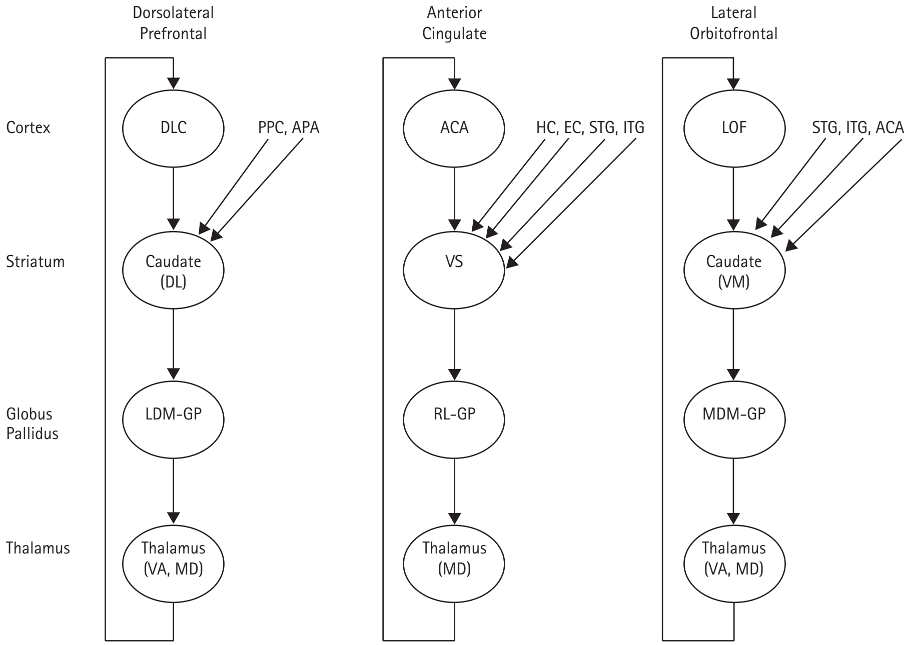

FIGURE 33.1. Proposed frontal-subcortical circuits implicated in cognition and emotion The indirect circuits and connections of the substantia nigra and subthalamic nucleus are not shown.

Abbreviations: ACA = anterior cingulate area; APA = arcuate premotor area; EC = entorhinal cortex; DLC = dorsolateral prefrontal cortex; GP = globus pallidus; HC = hippocampal cortex; ITG = inferior temporal gyrus; LDM = lateral dorsomedial LOF = lateral orbitofrontal cortex; MD = medial dorsal; MDM = medial dorsomedial; PPC = posterior parietal cortex; RL = rostrolateral; STG = superior temporal gyrus; VA = ventral anterior; VS = ventral striatum.

Source: Modified from Alexander et al. (1986).

circuit including the pre-Supplementary Motor Area (SMA), dorsal caudate–ventral thalamus involved in lexical retrieval and selection (discussed further in the following). There is also growing evidence of a circuit connecting the BG and Broca's area, and it has been hypothesized that such a circuit may influence grammar processing (e.g., Ullman, 2006). Lehericy et al. (2004) provide evidence for such a circuit involving the caudate and left BA 45, and Teichmann et al. (2015) found support for the notion that this circuit may be involved in syntax. Ford et al. (2013) also identified structural connections between the striatum, thalamus, and Broca's area; however, it was the putamen rather than caudate that showed structural connectivity with the left inferior frontal gyrus (IFG).

Studies of functional connectivity also provide insights into the possible role of subcortical-cortical circuitry in language. Snijders, Petersson, & Hagoort (2010) identified increased effective connectivity between the striatum and left IFG and middle temporal gyrus (MTG) during combination of lexical-syntactic representations. A large-scale (970 participants) resting-state functional connectivity study of language networks also demonstrated connectivity between Broca's and Wernicke's areas and bilateral caudate and left putamen/globus pallidus, ventral thalamus, and the STN (Tomasi & Volkow, 2012). There is also emerging evidence that different circuits may be engaged depending on the particular language function examined. Specifically, Jeon et al. (2014) recently observed different cortical-subcortical circuitry for second-language learning, depending on the form of processing involved (contextual, episodic, branching), with higher-level cognitive operations engaging the ventro-anterior prefrontal cortex, head of the caudate nucleus, and ventral anterior thalamus, while lower-level operations involved the posterior prefrontal cortex, body of the caudate, and medial dorsal nucleus of the thalamus (see Green & Kroll, Chapter 11 in this volume). Importantly, structural connectivity between components of these different circuits was confirmed with diffusion MRI, and similar patterns of activity were observed in parallel non-linguistic tasks employing a similar cognitive hierarchy.

Within the striatum, the caudate and putamen have traditionally been associated with cognitive and motor functions, respectively (and associative and motor circuits), suggesting a more likely influence of the caudate on language functions; however, this assumption needs revising. In particular, there is imaging evidence of putamen activity during cognitive tasks, co-activation of the putamen and prefrontal cortex, and anatomical projections connecting the putamen and cortical regions associated with cognition (Selemon & Goldman-Rakic, 1985) and language, including Broca's area (Ford et al., 2013; Provost, Hanganu, & Monchi, 2015). Intriguingly, examination of co-activation data from 5,809 human imaging studies recently identified the anterior putamen as being associated with social and language-related functions (Pauli, O'Reilly, Yarkoni, & Wager, 2016), although some identified terms such as "vocal" may reflect motor rather than language functions, consistent with evidence for the role of the putamen in speech production observed in both healthy and stroke populations (e.g. Seghier, Bagdasaryan, Jung, & Price, 2014).

Taken together, there is growing evidence of functional and structural connectivity between the striatum, thalamus, and cortical regions involved in language processing, beyond the established cortical-subcortical loops (Alexander, DeLong, & Strick, 1986). However, it is also important to be cautious regarding neuroanatomical assumptions for cortical-subcortical circuitry involving segregated parallel circuitry. Nambu (2008) argues that these loops may be considered on a continuum, rather than as segregated parallel circuits with distinct components, given evidence of convergence particularly in cortical-striatal inputs (e.g., Haber, Fudge, & McFarland, 2000). Based on a comprehensive review of these data, Bell and Shine (2016) propose that we need to consider both segregated and integrated BG-cortical circuitry. It has also been proposed that the direct/indirect pathway model is oversimplified and that functions of the direct, indirect, and hyperdirect components are not well established (Nambu, 2008), although there have been proposals regarding potential functions relevant to language function that may be carried out by these different components, which require further examination (Chenery, Angwin, & Copland, 2008; Crosson, Benjamin, & Levy, 2007). We now turn to evidence for a subcortical contribution to different aspects of language processing, taking into account neurological patient studies and functional neuroimaging evidence.

The Thalamus and Semantic Engagement

While there remains considerable controversy regarding the role of the BG in language, converging lesion, stimulation, and healthy neuroimaging evidence for thalamic contributions to lexical-semantic function is considerable. Yet the traditional method of clinical-anatomical correlations has also proven difficult with regard to thalamic aphasia. While thalamic aphasia has been described predominantly in terms of word-finding difficulties and semantic paraphasia (Crosson, 1992) and these features are often observed following thalamic hemorrhage, it has been challenging to isolate these features to particular regions of the thalamus based on evidence from thalamic infarcts (Crosson, 2013). Nadeau and Crosson (1997) proposed that lexical-semantic disturbances arise when (a) lesions involve the pulvinar-lateral posterior complex (which has connections with temporo-parietal and frontal regions relevant to language), or (b) there is a disruption to the frontal lobe–nucleus reticularis thalami (NR) system. There is considerable evidence supporting the role of the pulvinar and lateral-posterior complex in lexical-semantics, and neuroanatomically these regions have connections with cortical regions involved in language processing. Evidence from ventral anterior and ventrolateral nuclei suggests a more minor role (Nadeau & Crosson, 1997) while other more recent proposals suggest that the ventral anterior nuclei play a role within BG-thalamic-cortical circuits relevant to word retrieval (Crosson, 2013).

There has also been a more recent revision of certain anatomical assumptions of this selective engagement model (Crosson, 2013), suggesting involvement of the pulvinar as critical, while the roles of the centromedian and parafasciculus nuclei are less clear.

The proposed role of the thalamus in language is conceived as one of "selective engagement." More specifically, it involves the temporary engagement of language-relevant cortical networks, which is conceptualized as intentionally guided attention and also resembles working memory processes in some respects (Nadeau & Crosson, 1997). This selective engagement has been primarily demonstrated with respect to lexical-semantic operations and word finding. It may be applied to the process of confrontation naming, where the detailed patient study of Raymer, Moberg, Crosson, Nadeau, & Gonzalez-Rothi (1997) supports the view that while semantic and lexical systems may be intact following left thalamic lesions, the selective engagement of mappings from semantics to lexical representations may be compromised. Evidence of category-specific naming deficits following a hemorrhagic lesion involving the pulvinar further supports the view that discrete thalamic-cortical connections may result in such specific naming deficits (Nadeau & Crosson, 1997). Later revisions of this model also emphasize the language-relevant involvement of the thalamus (and pulvinar in particular) in transferring or relaying information between distinct cortical regions (including via cortico-thalamo cortical circuits) (Crosson, 2013). Crosson (2013) provides a comprehensive integrated review and proposal, including the suggestion that cortico-thalamic feedback from layer 6 cells to thalamic nuclei, which serves to sharpen the focus of representations, may also play a role in language function. Electrical stimulation studies also support the view that the cortical-pulvinar-cortical projection system supports cortical synchronization involved in word retrieval, with stimulation leading to anomia (Hebb & Ojemann, 2013). This role may not be limited to output, however, with evidence from simultaneous thalamic and scalp electrode recordings showing activity relating to the processing of semantic anomalies in sentences (Wahl et al., 2008). While the semantic engagement model of Nadeau and Crosson (1997) proposed a role for the thalamus in language that was independent of the BG, later revisions also propose a role for the thalamus in BG-thalamic-cortical circuits involved in lexical selection (Crosson, 2013).

The role of the thalamus and more specifically the pulvinar in semantic processing was further emphasized by Hart and colleagues (Kraut et al., 2002; Hart et al., 2013), who have proposed a "neural hybrid model of semantic memory." This model is based on patient studies (including electrode recordings) and neuroimaging in healthy individuals and is generally consistent with the proposed role of the thalamus in semantic engagement (Nadeau & Crosson, 1997). According to this proposal, thalamic activity is critical to semantic feature binding, being linked to similar activity in a number of cortical regions when combining multiple semantic features to retrieve an object representation. Subsequent development of this model suggested a pre-SMA–thalamic–caudate circuit involved in semantic object retrieval, which is supported by activity observed in these regions (in addition to the ventral temporal-occipital lobes associated with visual memory) during an fMRI study of semantic object retrieval (e.g., Kraut et al., 2002). During correct object retrieval, there is a high beta-band power increase which is consistent with synchronization and communication between the pre-SMA and thalamus. This circuit is assumed to be engaged during controlled semantic retrieval and search, and the role of the caudate within this model is to select the correct semantic object and suppress incorrect representations, which broadly agrees with other proposals that the striatum is involved in selection and suppression during word production (Crosson et al., 2003) and during lexical ambiguity resolution (Copland, 2003). The combined role of the striatum and thalamus may also extend to new word learning, where it has been proposed that they form part of a network that selects the appropriate meaning from competing representations and associates this meaning with the new word form (Ye, Mestres-Misse, Rodriguez-Fornells, & Munte, 2011).

The Basal Ganglia, Phonology, and Lexical-Semantic Processing

The involvement of the BG in language operations will be considered in part on the basis of studies in Parkinson's disease (PD), given its association with impaired striatal output due to degeneration of the nigrostriatal system (Gerfen, 1992). Similarly, studies of Huntington's disease (HD) have been used to examine the role of the caudate in phonology and lexical-semantics. However, it is important to be cautious when making inferences regarding BG function based only on observations in these populations without direct measures of BG function, given that pathology is not limited to these structures (e.g., Rüb et al., 2016).

While the majority of work on possible BG contributions has focused on lexical-semantics and sentence-level functions, there is some direct evidence for the role of the striatum in phonological processing. Tettamanti et al. (2005) utilized positron emission tomography (PET) to investigate dopamine binding to D2 receptors in healthy adults during the detection of phonological and syntactic anomalies within pseudo-word sentences. Phonological processing accuracy correlated with tracer binding potential in the left caudate, while reaction times correlated with tracer binding potential in the left putamen. These findings indicated that more accurate and faster phonological processing was associated with reduced dopamine requirements in the left BG.

Research in PD further implicates a role for BG circuitry in phonological processing, with evidence of phonological processing deficits in this population (Elorriaga-Santiago, Silva-Pereyra, Rodriguez-Camacho, & Carrasco-Vargos, 2013). Moreover, recordings of neuronal activity from depth electrodes in PD patients have indicated that activity in the right caudate may be linked to aspects of phonological processing (Abdullaev & Melnichuk, 1997), while recordings of local field potentials from the STN in PD have revealed auditory evoked potentials in response to early stage auditory perception, most likely related to phonological processing (De Letter et al., 2014). Teichmann, Darcy, Bachoud-Levi, & Dupoux (2009) also demonstrated that although phoneme perception for isolated words was intact in patients with HD, phoneme discrimination deficits were evident within phrasal contexts. The researchers suggested that these results may reflect a role for the striatum in phonological short-term memory, which is required for word perception in phrasal contexts.

There is considerable evidence that various aspects of lexical-semantic processing are altered in PD. In particular, the use of semantic priming tasks has shed light on a wide array of lexical-semantic disturbances in PD, which may be linked to dysfunction within BG circuitry. Semantic priming refers to the well-recognized phenomenon whereby a target word is recognized faster (e.g., during a lexical decision) when preceded by a related prime word (e.g., *winter-snow*) relative to an unrelated word (e.g., *window-snow*). Semantic priming effects can be a result of automatic spreading activation (Collins & Loftus, 1975; Neely, 1977), such that activation of a prime word leads to a spread of activation throughout the semantic network, which partially activates other semantically or associatively related concepts. This spreading of activation subsequently results in faster recognition of target words related to the prime relative to targets that are unrelated. Accordingly, the time course of automatic semantic activation can be charted by manipulating the amount of time that elapses between the prime and target, known as the stimulus onset asynchrony (SOA) or inter-stimulus interval (ISI). In addition to automatic semantic activation, however, it is possible for conscious processes such as prelexical expectancies or post-lexical semantic matching strategies (see Neely, 1991, for a review) to induce semantic priming effects.

Numerous semantic priming studies have provided evidence for a delayed time course of semantic activation for some patients with PD, as evidenced by the emergence of semantic priming effects only at longer SOAs (Angwin, Chenery, Copland, Murdoch, & Silburn, 2007; Angwin et al., 2009; Arnott, Chenery, Murdoch, & Silburn, 2001; Grossman, Lee, Morris, Stern, Hurtig, 2002). As suggested by Grossman et al. (2002), such delays to lexical access in PD may be due to dysfunction within dopamine-dependent frontal-striatal circuitry that supports information-processing speed. Such claims are further supported by an absence of semantic priming in PD patients tested when off their levodopa medication (Angwin et al., 2007, 2009), PET research showing that cognitive slowing in PD is linked to dopaminergic dysfunction in fronto-striatal circuitry (Jokinen et al., 2013), and suggestions of a faster time course of semantic activation in healthy adults who have been administered levodopa relative to those on placebo (Angwin et al., 2004). Hence, the extent to which automatic semantic activation is disturbed for an individual with PD may be modulated by the magnitude of BG dysfunction for that person, although this proposal relies on indirect evidence. This notion would explain why automatic semantic priming appears intact in some studies of PD (Copland, 2003; Filoteo et al., 2003), as the extent of BG dysfunction for some patients may not be sufficient at the time of testing to induce changes to the temporal course of lexical access.

Besides influencing the speed of lexical access, the BG may also contribute to semantic inhibitory processes and the selection of lexical items from competing alternatives. Research on the processing of lexically ambiguous words (e.g., *bank*) has provided insights into the role of the BG in such aspects of language processing. Copland (2003) examined semantic priming for ambiguous words in people with PD, people with non-thalamic vascular subcortical lesions, and healthy controls. Target words were related to either the dominant (*bank-money*) or subordinate (*bank-river*) meaning of the ambiguous prime word, or were unrelated. While all groups demonstrated priming of both meanings at a short ISI, a different pattern between groups emerged at the long ISI. Specifically, at a long ISI it is expected that attentional resources will be directed toward the dominant meaning of the ambiguity, such that priming should only be observed for the dominant meaning and not the subordinate meaning. While this pattern of priming at the long ISI was indeed observed in controls, the PD and subcortical stroke participants continued to demonstrate priming for both conditions. Similarly, other research has illustrated difficulties with the selective activation of the appropriate meaning of ambiguous words when presented within repeated, lexical, sentential, or discourse-based contexts for patients with PD and/or nonthalamic subcortical lesions (Copland, Chenery, & Murdoch, 2000a, 2000b; Copland, Chenery, & Murdoch, 2001; Copland, Sefe, Ashley, Hudson, & Chenery, 2009).

Chenery et al. (2008) sought to clarify the nature and involvement of the BG circuitry in the enhancement and suppression of ambiguous word meanings when presented within a linguistic context. Specifically, when processing ambiguous word pairs with a long ISI, Chenery et al. proposed that the inferior frontal BG circuitry is critical, with the direct pathway enhancing the processing of both dominant and subordinate meanings and the indirect pathway subsequently suppressing whichever meaning is contextually inappropriate. As mentioned earlier, there is mounting evidence of BG–inferior frontal circuitry (Ford et al., 2013), although the components of the striatum involved are not consistent with an exclusive role of the caudate in such language functions. Providing some support for this proposal, Ketteler et al. (2014), utilized fMRI to study ambiguity resolution in PD. Participants performed a semantic judgment task in which they were asked to decide whether the meanings of two words presented at the top of the screen both matched an ambiguous target word presented below. In the "yes" trials (referred to as the homonym condition), where both words were related to the target, one word was related to the dominant meaning and one word to the subordinate meaning of the target. There were three "no" conditions, consisting of either a dominant-related or subordinate-related word together with an unrelated distractor, or two unrelated distractors. In controls, bilateral caudate activation was evident for the homonym condition, and left caudate activity was evident in the dominant-distractor condition. PD patients demonstrated lower accuracy for the dominant-distractor and subordinate-distractor conditions relative to controls, and left caudate activity correlated positively with task accuracy for these two conditions in the PD group. However, these correlations were not observed in controls. Based on these findings, Ketteler et al. suggested that left caudate dysfunction may contribute to semantic meaning-integration deficits in PD. Importantly, there was no significant relationship between these findings and a measure of executive function, suggesting that this may not simply reflect broader cognitive deficits.

The proposed involvement of the BG in lexical ambiguity resolution most likely reflects a broader function in controlled processing, which includes semantics, a view supported by observations of increased caudate activity during semantic judgments and lexical decisions for non-ambiguous words (e.g., Abdullaev, Bechtereva, & Melnichuk, 1998; Binder et al., 2003; Binder et al., 1997; Kotz, Cappa, von Cramon, & Friederici, 2002). In production, Crosson et al. (2003) provided evidence for caudate activity in healthy subjects during selection for word production as part of a caudate–thalamic–pre-SMA circuit, while caudate activity has also been observed during word production that involves suppressing irrelevant words (Ali, Green, Kherif, Devlin, & Price, 2010), resolving semantic interference (Canini et al., 2016), and selection processes in sentence generation (Argyropoulos, Tremblay, & Small, 2013). Robles, Gatignol, Capelle, Mitchell, & Duffau (2005) found that stimulation of the head of the caudate caused perseveration during naming, consistent with a role in controlling the selection and inhibition of items during word production. In sum, these findings are consistent with the proposal that the striatum (and caudate in particular) is engaged during lexical-semantic tasks when controlled, as opposed to automatic, processing is required (Friederici, 2006). More specifically, different portions of the caudate may be engaged for different aspects of cognitive control (see Mestres-Misse, Turner, & Friederici, 2012). The proposed involvement of the BG in selecting and suppressing representations is consistent with a broader role in selecting motor representations (Mink, 1996) and in dopaminergic working memory operations (Bäckman & Nyberg, 2013).

The Basal Ganglia Contribution to Bilingualism and Language Learning

There is now considerable evidence that the proposed role of the BG in language control and in particular lexical selection (as discussed earlier) extends to bilingual language processing (see Green & Kroll, Chapter 11 in this volume). In bilingual speakers, it has been proposed that the BG govern controlled aspects of language processing, including language and lexical selection and switching (Abutalebi & Green, 2007). Crinion et al. (2006) provided compelling evidence that the left caudate monitors and controls switching of languages and meaning, as demonstrated in a cross-language semantic priming paradigm (see also Abutalebi & Green, 2007; Rüschemeyer, Fiebach, Kempe, & Friederici, 2005). This finding also converges with impaired language control observed in studies of bilingual patients with BG lesions (e.g., Abutalebi & Green, 2007; Calabria, Marne, Romero-Pinel, Juncadella, & Costa, 2014).

In addition to controlling bilingual language processing, the BG may contribute to aspects of language learning. There is already strong evidence for the role of the striatum in various forms of non-linguistic learning, including various forms of procedural, reward-based, probabilistic, and category learning (Packard & Knowlton, 2002). The proposed role of the BG in procedural learning system and grammar will be discussed later with respect to Ullman's (2001b) procedural/declarative model; however, the BG may also contribute to other forms of learning relevant to language acquisition. While contemporary models of language learning often focus predominantly on hippocampal-neocortical interactions driving language learning (Davis & Gaskell, 2009), Rodriguez-Fornells, Cunillera, Mestres-Misse, and de Diego-Balaguer, 2009 observe that the BG are connected to proposed networks responsible for various aspects of language learning, including (a) phonological storage and rehearsal, (b) meaning extraction, (c) an episodic-lexical interface dependent on the medial-temporal lobe, and (d) cognitive control and motivation, suggesting a possible integrative role in combining information from different sources. This role might relate to the gating and selection of appropriate representations, as proposed elsewhere in a non-learning context (Crosson et al, 2003). Consistent with this proposal, Ye et al. (2011) recently observed the involvement of the caudate in a network including the left IFG, middle frontal gyrus (MFG), and thalamus that was engaged when selecting appropriate meanings to associate with a new word representation, while a separate network (not including the caudate) was involved in integrating the word into a sentential context. Acquisition studies that do not involve semantic learning typically do not show BG activity (see Davis & Gaskell, 2009), further supporting the notion that the BG contribute to developing associations between semantic and new lexical representations.

With regard to the specific components of the BG involved in language learning, this most likely varies, depending on the aspect of learning engaged, as demonstrated by Jeon et al. (2014). Intriguingly, the act of learning new word meanings in context also appears to engage the ventral striatum, suggesting a role for reward systems in this process (Ripolle et al., 2014). While not explicitly manipulating reward, Ripolle et al. (2014) convincingly demonstrated that successful learning of new words in a sentence context was dependent on the ventral striatum, with a non-linguistic reward task showing activation in the same region, leading the authors to suggest that word learning under these conditions is intrinsically rewarding and dependent on these subcortical systems. A subsequent study lent further credence to this proposal, demonstrating that successful learning of words and activation of the ventral striatum (as part of a midbrain–ventral striatum–hippocampus circuit) was associated with increased pleasantness ratings and physiological responses consistent with increased intrinsic reward (Ripolle et al., 2016). Ventral striatum activity also appears important to other aspects of semantic processing that are intrinsically rewarding, such as the appreciation of humor (Bekinschtein, Davis, Rodd, & Owen, 2011). There is also an increasing appreciation of the role of the BG in language learning, based on evidence that children with language learning difficulties show structural subcortical abnormalities (particularly in the caudate) and impairments in more domain general–procedural aspects of learning assumed to involve the striatum (see Krishnan, Watkins, & Bishop, 2016). It is important to note that some of the strongest evidence for subcortical contributions to language learning have also demonstrated that this role reflects a broader role in similar forms of learning (Jeon et al., 2014; Ripolle et al., 2014).

The Basal Ganglia and Verb Processing

There is now a body of work suggesting that BG dysfunction (particularly as observed in PD) is associated with a selective impairment of action/verb processing, although the selectivity of this proposal is at odds with evidence of general lexical-semantic deficits associated with PD and BG lesions (discussed earlier). This view has been supported by evidence of deficits in verb generation, action naming, and action verbal fluency, together with observations of increased deficits in PD patients off levodopa medication (see Cardona et al., 2013, for a review). Importantly, recent evidence also suggests that impairments to action naming and action semantics in PD occur independently of executive function deficits (Bocanegra et al., 2015). While claims have been made that such deficits relate to motor impairments in PD, it should be noted that the relationship between verb processing and motor circuitry is not well established. Some novel insights were provided by Peran et al. (2013), who observed increased activation within the premotor cortex for PD patients on versus off levodopa during action word generation, which was interpreted as consistent with levodopa enhancing activity within the motor putaminal cortical striatal loop during action semantic processing. The functional significance of this brain activity is also difficult to interpret, given that there were no behavioral changes on versus off levodopa for action word generation. More recently, Herrera, Bermudez-Margaretto, Ribacoba, and Cuetos. (2015) tested action verbal fluency in PD patients on and off medication and examined the semantic-motor meaning of the movement verbs that patients generated during task performance. The movement verbs were classified as those with a higher motor specificity (i.e., those that denoted an action performed with small parts of the body, e.g., sew, knit) versus those with a lower motor specificity (i.e., those denoting actions that included the whole body, e.g., swim, run). Herrera et al. found that both controls and PD patients on dopamine medication produced more verbs with a high motor specificity compared to when the patients were tested off medication.

However, it should be noted that discrepancies remain on the particular question of verb processing in PD. For instance, while Fernandino et al. (2013) observed impaired processing of action but not abstract verbs, compared to controls, Kemmerer et al. (2013) found no significant difference between controls and PD patients (both on and off dopaminergic medication) when processing action and abstract verbs, besides an overall slowing in RTs regardless of verb type (see Kemmerer, Miller, MacPherson, Huber, & Tranel, 2013, for a critique of the Fernandino et al., 2013, study).

Studies investigating a phenomenon known as the action compatibility effect (ACE) have also suggested the potential role of BG circuitry in action processing. During an ACE task, participants are required to listen to sentences and press a button upon comprehension of each sentence. Sentences either describe an action performed with an open hand, describe an action performed with a closed hand, or do not describe a hand action (neutral sentences). Critical to the ACE task is the nature of the button press response. In some blocks of trials, participants must press the button with an open hand, and in other blocks it must be pressed with a closed hand. Accordingly, this creates compatible trials (i.e., an open-hand sentence/response or closed-hand sentence/response), incompatible trials (i.e., an open-hand sentence and closed-hand response or vice versa) and neutral trials (i.e., a neutral sentence paired with either type of response).

In healthy adults, the ACE effect refers to longer reaction times for incompatible relative to compatible trials; however, Ibanez et al. (2013) observed an absence of the ACE effect in early PD patients. This deficit appeared inconsistent with a general motor or language impairment in PD, however, a post hoc item analysis found that increased errors on a test of verb-action comprehension for trials related to hand actions was associated with a reduced ACE effect in PD. This correlation was not evident for errors made on trials unrelated to hand actions. It should be noted that this post hoc item-based analysis did not allow for matching of these categories on other important variables that may also influence performance. Research also indicates the ACE effect is absent in people with HD as well as their first-degree relatives (Kargieman et al., 2014).

Cardona et al. (2013) have proposed that BG-thalamo-cortical circuitry, with distinct motor versus semantic circuits, may modulate the motor-language interaction evident during action/verb processing. Specifically, a frontal circuit would be involved in the processing of motor simulation and action patterns associated with the meaning of verbs. A temporal circuit would be involved in abstract conceptual knowledge and could directly impact semantic processing in areas including the anterior temporal lobe and superior temporal sulcus. Further evidence provided in support of this proposal comes from neuroimaging and deep brain stimulation (DBS). Measurement of event-related potentials (ERPs; see Leckey & Federmeier, Chapter 3 in this volume) has shown aberrant motor potentials in PD relative to controls during performance of the ACE task (Melloni et al., 2015). In both PD and controls, this motor potential effect was associated with gray matter volume in bilateral BG structures, including the putamen, caudate nucleus, and globus pallidus. Moreover, increased BG atrophy in PD was correlated with increased impairments to the motor potential. These findings supported Cardona et al.'s proposed role of the BG in motor-language coupling through its involvement in frontotemporal circuitry. The behavioral significance of these findings remains unclear, however, given that the relationship between the behavioral ACE effect and the MRI and ERP results was not tested in this study.

In a study of action and object naming in PD patients with DBS of the STN, Silveri et al. (2012) found that while the accuracy and speed of action naming in PD patients on stimulation did not differ to controls, the PD patients off stimulation were slower and less accurate than controls. PD patients off DBS were also slower to name actions relative to objects, while no difference was evident for controls or patients on stimulation. Moreover, Silveri et al. also observed qualitative differences in naming performance between PD patients on versus off stimulation, with fewer semantic errors evident for patients on stimulation. Silveri et al. suggested that stimulation may restore activity within the cortico-striatal circuits necessary for retrieval and selection of lexical-semantic information; however, the implications for proposals regarding verb-specific processing and the BG are unclear, as direct comparisons for on versus off stimulation showed faster and more accurate naming regardless of action versus objects.

Subcortical Contributions to Sentence and Grammatical Processing

Relative to healthy adults, difficulties processing complex sentences are more pronounced for some patients with PD (Grossman et al., 2000; Kemmerer, 1999; Lee, Grossman, Morris, Stern, & Hurtig, 2003; Natsopoulos et al., 1991). While some researchers have postulated that sentence comprehension impairments in PD stem from grammatical processing deficits (Lieberman et al., 1992; Natsopoulos et al., 1991; Natsopoulos et al., 1993), others have attributed the deficits to limitations in the availability of cognitive resources, including working memory (Geyer & Grossman, 1994; Grossman, Lee, Morris, Stern, & Hurtig, 2002; Kemmerer, 1999; McNamara, Krueger, O'Quin, Clark, & Durso, 1996), attention (Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Lee et al., 2003), and/or information-processing speed (Grossman, Zurif, et al., 2002; Lee et al., 2003).

A related account based on healthy neuroimaging proposes that the striatum contributes to a cortical syntactic unification network (involving the left IFG and left MTG) by influencing the selection of lexical-syntactic representations (Snijders et al., 2010; Hagoort, 2005). It is argued that the striatum provides a gating mechanism for working memory, supporting the extraction of these representations from the left MTG for the unification operations carried out by the left IFG. Accordingly, presentation of ambiguous sentences is associated with increased co-activation of the striatum, MTG, and left IFG. Snijders et al. (2010) hypothesize that ambiguous sentences represent salient events that cause dopamine release, with this signal allowing the striatum to modulate cortical transfer of lexical-syntactic information. Although the role of dopamine in this process remains to be verified, there is supporting evidence for the broader role of the striatum in updating working memory and selecting/suppressing competing representations (Cools, 2011), including lexical items for production (Crosson et al., 2007).

The declarative/procedural model proposed by Ullman and colleagues (Ullman, 2001a, 2001b; Ullman et al., 1997) is another model that may be applicable to the sentence-processing deficits in PD and favors the notion that the subcortex contributes to grammatical processing. According to this model, the declarative memory system underlies the mental lexicon, storing knowledge of the sounds and meanings of words, and is subserved by a medial temporal circuit. The procedural memory system, on the other hand, is subserved by frontal/BG structures and may underlie the learning and expression of grammatical rules. Thus, the model predicts that irregular verbs (e.g., *bring-brought*), which constitute a fixed list and do not involve overt manipulation of morphological rules, will be stored in the declarative system. In contrast, the procedural system may be important for rule-based building of grammatical structures such as regular verbs (e.g., *walk-walked*), since the learning and computation of these structures is dependent on morphological sequencing (e.g., *walked* = *walk* + *ed*). Ullman proposed that given the subcortical degeneration in PD, impairment to the procedural system would be expected, while the declarative system should be unaffected.

In support of this theory, Ullman et al. (1997) found that PD patients experienced greater difficulties producing regular past-tense verbs compared to irregular past-tense verbs. Accordingly, it may be argued that sentence-processing deficits in PD are related to a general inability to apply such procedural rules of grammar. A number of other researchers have also attributed sentence-processing difficulties in PD to specific grammatical parsing deficits. Lieberman et al. (1992) found that PD patients' sentence comprehension was impaired on a sentence-picture-matching task, and that the magnitude of this impairment was a function of both the stage of PD and the complexity of the sentence. It was argued that these deficits might reflect impairment in the ability to apply the rules of syntax appropriately. Similarly, Natsopoulos et al. (1991, 1993) also observed that PD patients experienced difficulties comprehending complex sentences as measured by a sentence-picture-matching task. More important, the researchers illustrated that the PD patients often assigned the noun phrase (NP) closest to the relative clause verb as the subject of that relative clause, suggesting that PD patients may rely on some form of minimal distance principle to aid in comprehension. In terms of language production, Phillips et al. (2012) observed a decline in accuracy and response time for the production of regular past-tense verbs when the patients were on relative to off DBS. This finding suggests that STN stimulation has a negative impact on grammatical aspects of language processing and implicates BG circuitry.

However, Ullman's proposed role for the BG in grammatical processing was challenged in a convincing fashion by Longworth, Keenan, Barker, Marslen-Wilson, and Tyler (2005), who found that the ability to inflect regular verbs was not significantly more impaired than the ability to inflect irregular verbs for patients with PD, HD, and vascular lesions of the striatum, suggesting that BG disorders are not associated with a selective deficit for regular inflectional morphology. Penke, Janssen, Indefrey, & Reitz (2005) also observed no evidence supporting a deficit in processing grammatical rules in German PD patients. Certainly, this raises doubts over whether the sentence-processing deficits in PD are related to dysfunctional application of grammatical rules. Longworth et al. (2005) instead found that subcortical dysfunction was associated with an impairment in later language processes involving the selection and inhibition of competing alternatives, consistent with a broader role for the BG in selection and suppression in both language and non-language domains, as described elsewhere (Copland, 2003; Crosson et al., 2003).

Deficits to lexical access as a result of BG dysfunction in PD may have subsequent downstream consequences for sentence comprehension. Numerous studies have illustrated longer delays to lexical-semantic activation in PD patients, with increased difficulties comprehending complex sentences (Angwin, Chenery, Copland, Murdoch, & Silburn, 2005; Angwin et al., 2007; Grossman et al., 2002). Other research has found that sentence comprehension impairments in PD are not specific to more complex constructions, but rather that PD is associated with a more generalized sentence comprehension impairment that is likely dependent on executive function (Colman et al., 2011).

In an fMRI study, Grossman et al. (2003) observed reduced striatal recruitment in PD patients during the processing of complex sentences. More recently, Ye et al. (2012) observed increased caudate activation in healthy controls during the processing of more complex sentences, consistent with the increased processing demands associated with these sentences. In contrast, the PD group demonstrated the opposite pattern, with increased caudate activation for the less demanding sentence type.

Plausibility judgments for idiomatic ambiguous sentences have been shown to be reduced in PD patients tested off medication, which may be consistent with reduced availability of cognitive resources to support interpretation when off medication (Papagno, Mattavelli, Cattaneo, Romito, & Albanese, 2013). Other research, however, indicates that the contribution of the striatum to sentence processing is not constrained purely to the modulation of lexical access or the availability of general cognitive resources such as working memory. Sambin et al. (2012) demonstrated that patients with HD experience specific difficulties applying infrequently used syntactic operations to appropriate sentence contexts. Specifically, while HD patients established a co-reference between a name and a pronoun in an ambiguous sentence such as "Paul smiled when he entered," where "Paul" and "he" can potentially refer to the same person, the HD patients failed to appropriately block such a co-referential interpretation when presented with a sentence such as "He smiled when Paul entered." These deficits were observed despite the normal performance of the HD patients during processing of right branching and center-embedded relative sentences, suggesting that working memory deficits cannot account for the observed syntactic processing difficulties. Such findings led Sambin et al. to propose that the HD patients may have a deficit in the ability to inhibit or switch from frequently used to infrequent syntactic operations. This account is consistent with previously noted proposals that the striatum serves to suppress competing alternatives in lexical-semantic processing (e.g., Copland, 2003). Impaired language-related rule application and lexical processing in HD have also been shown to correlate with dissociable components of the BG (Teichmann et al., 2008). Specifically, aspects of lexical processing correlated with dorsal portions of the caudate and more ventral portions of the caudate and putamen for aspects of rule application. More recently, Teichmann observed that impairments with complex syntax comprehension following surgical frontal-striatal lesions were associated with damage to a tract connecting the left caudate head with left IFG (BA 45).

Utilizing the measurement of event-related potentials during sentence processing, Friederici, Rüschemeyer, Hahne, and Fiebach (2003) found that early automatic syntactic processes, as indexed by the early negativity, were intact in PD. In contrast, however, the P600 component was reduced in PD relative to healthy controls in response to processing of phrase structure violations, suggesting that the BG support late processes of syntactic integration during sentence comprehension. Providing further support for this interpretation, ERP research has also documented that verb-argument structure violations elicit a P600 in patients with lesions that exclude the BG, whereas this component is absent in patients with BG lesions (Kotz, Frisch, Von Cramon, & Friederici, 2003). Subsequent work suggested that this finding was not due to a more generalized deficit in controlled or attentional processing (see Kotz, Schwartze, & Schmidt-Kassow, 2009). Instead, an intriguing alternative proposal suggested that these syntax deficits are secondary to dysfunction in a medial pre-SMA–BG circuit that processes temporal variations or patterns in the auditory speech signal, and making predictions in speech comprehension (Kotz et al., 2009), reflecting a broader role in sequencing and temporal processing.

CONCLUSION

There have been considerable advances in our understanding of functional and structural cortical-subcortical connectivity that further implicates subcortical structures in language-relevant processes, and there is a growing appreciation that traditional notions of a series of functionally and anatomically segregated subcortical-cortical loops need to be revised. The current review did not consider in-depth evidence from the burgeoning area of DBS in PD, which has recently provided numerous studies in how striato-cortical circuit modulation may influence language processing, as this effort has yielded a highly variable and at times conflicting set of observations. This includes improvements (Castner et al., 2007; Zanini et al., 2002), impairments (Castner et al., 2008; Parsons, Rogers, Braaten, Woods, & Troster, 2006), and no influence (Batens et al., 2014; Castner et al., 2007; Tremblay et al., 2015) on various aspects of language, suggesting the need to better understand and identify the actions of DBS on specific cortical and subcortical components and circuits and the need to account for factors such as laterality, disease duration, and levodopa, before we can meaningfully interpret behavioral effects.

Based on patient and healthy neuroimaging studies, there is mounting evidence for the contribution of the thalamus and striatum to various aspects of language function beyond initial proposals based on clinical-anatomical correlations. However, evidence for a unique and specific role for the BG in language remains uncertain, with mixed findings, for instance, regarding a proposed selective role in action-verb processing. Instead, there is considerable evidence from patient studies and neuroimaging in healthy individuals consistent with domain-general role of the thalamus in attentional engagement and working memory (seen in semantic processing) and for striatal-thalamic-cortical circuits in cognitive control, as demonstrated in the selection and suppression of representations, which impacts on word selection (in production and comprehension), bilingual language processing, and sentence comprehension. There are emerging theories suggesting that other general subcortical functions relating to learning, temporal processing, and sequencing may also influence language processing. Combined neuroimaging and patient studies in addition to research investigating dopaminergic and genetic contributions to the language-relevant subcortical mechanisms are also likely to shed further light on how these regions modulate language function across a range of populations.

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CHAPTER 34

LATERALIZATION OF LANGUAGE

LISE VAN DER HAEGEN AND QING CAI

INTRODUCTION

THOUSANDS of researchers are accumulating knowledge concerning how language is processed in the human brain. It is such a fascinating topic because it is considered to be one of the traits that makes humans unique. Moreover, the specialization to one cerebral hemisphere is extraordinary: about 95% of right-handers and 75% of left-handers dominantly activate their left hemisphere (LH) during speech production, whereas the remainder of humans shows an atypical right hemispheric (RH) dominance or bilateral organization (Knecht et al., 2000). However, it is not the ability to communicate that differentiates humans from other animals, nor can language dominance be selectively attributed to humans. Vocal expressions and other communicative gestures are equally left lateralized in birds, mice, and nonhuman primates (Rogers & Andrews, 2002). It is the intriguing joint dominance of right-handedness and LH speech lateralization that has led to the abundance of language lateralization research in the human brain.

Let us introduce this chapter with the dominating question: Are handedness and language lateralization linked? This is an ongoing debate, but recent evidence points to an indirect relationship between these phenotypes. A common underlying origin was first suggested by the higher incidence of aphasia in right-handers than left-handers after unilateral LH brain damage (Benson & Geschwind, 1985; Hécaen & Sauguet, 1971). Evidence for an influence of handedness on language laterality was further provided by long-believed single-gene theories. For example, the right-shift gene theory posits that an RS + allele leads to right-handedness and LH language dominance, whereas an RS – allele randomly assigns handedness and language dominance. The combination of the two alleles most likely results in typical LH language dominant right-handers (Annett, 1998). Single-gene theories, however, have been refuted because evidence from most recent studies clearly shows that both handedness and language dominance are determined by multiple genes, with so far no candidate genes common to both functions (e.g., *LRRTM1* [Francks et al., 2007] and *PCSK6* [Brandler et al., 2013] for handedness, and *FOXP2* for language dominance [Ocklenburg et al., 2013; Pinel et al., 2012]). Still, the prevalence of LH language lateralization in right-handers compared to left-handers appears to be too high to be incidental. Differences in research approaches may explain why this puzzling coherence has not been unraveled yet. For example, evolutionary research suggests that the nature of manual actions must be taken into account. Language dominance may be linked to the lateralization of communicative gestures, but not to noncommunicative manual actions, such as grasping an object (Cochet, 2015). In language laterality research, however, handedness scores are often derived from the Edinburgh Handedness Inventory, asking manual preference for daily noncommunicative actions (Oldfield, 1971). Another possibility is that alternative measures of handedness, such as familial sinistrality, are more closely related to language lateralization. For example, having a left-handed first-degree relative reduced the surface area of the planum temporale in the LH up to 10%, independently of the individual's own handedness, in Tzourio-Mazoyer, Simon, et al. (2010). Finally, the degree, apart from direction, of handedness and language lateralization may also play a role in the link between both phenotypes (Mazoyer et al., 2014).

Despite the unclear role of handedness in language lateralization, left-handers are considered an interesting sample when studying cerebral asymmetries. It is wrong to take them as a homogeneous atypical group based on their handedness because the majority of them still show typical LH language dominance (see the following section), but some are RH language dominant. Their heterogeneity provides a unique perspective on how cognitive functions are related in healthy participants. If, for example, speech production shifts to the RH, related functions are expected to lateralize to the same atypical side in order to optimize information exchange, whereas unrelated functions reside in the contralateral hemisphere (Willems, Van der Haegen, Fisher, & Francks, 2014). Language laterality can be an ideal starting point to reveal interactions between cognitive functions such as cognitive control, memory, and so on, because it is the most well-documented lateralized function until now (Cai & Van der Haegen, 2015). Studies including left-handers with or without known atypical lateralization will therefore be extensively reviewed in this chapter, even though one should bear in mind that handedness correlates with language lateralization without revealing direct causes.

Lateralization research is, of course, far from limited to a comparison between right- and left-handers. A long history of research made clear that language lateralization is influenced by anatomical, evolutionary, genetic, developmental, and experiential factors, and impairment; some of these factors were already introduced earlier. We will briefly describe evolutionary and anatomical influences on language lateralization in general in this introduction. More detailed studies investigating the influence of these factors on language sub-processes will be discussed in further sections. Evolutionary, hemispheric specialization might have arisen when the cortex expanded and unilateral specialized regions became more advantageous than redundant processing of the same function in homologue areas in the LH and RH. In an increased brain volume, intra-hemispheric processing facilitates information exchange between connected brain regions. Moreover, lateralization increases brain capacity by creating cortical space available for other cognitive functions. In particular, the expansion of the frontal cortex in primates, housing Broca's area (involved in speech production), may have contributed to language asymmetry (Toga & Thompson, 2003; see also Corballis, 2009; Hopkins & Cantalupo, 2008). Anatomically, three remarkable asymmetries have consistently been observed. First, the so-called right frontal and left occipital petalias refer to the anterior extension of the RH beyond the LH and the occipital protrusion of the LH beyond the RH. In addition, RH frontal and LH occipital areas are wider. Second, the Sylvian fissure runs more anteriorly and steeper in the RH than LH. Third and presumably most important for language lateralization, the planum temporale is about 35% larger on the left side (Toga & Thompson, 2003; see also Hugdahl, 2011).

An important note is that so far, we have collapsed lateralization findings across language functions. A large part of the literature has indeed long treated language as one unitary function, mostly taking the asymmetry of speech production as an equivalent of language lateralization. It became clear, however, that language processing is much more complex: The focus of neurocognitive research has shifted from identifying individual neural nodes to structural and functional networks, and not all language sub-processes are lateralized to the same degree or even in the same direction. We will therefore review lateralization in more detail by discussing the sub-processes. We will first give an overview of the most important recent studies on the lateralization of speech production, auditory speech processing, and reading, as these are considered to be the three core sub-processes of language. We limit this chapter to higher-order processes, as the low-level stages of language in the primary auditory and visual cortex are not lateralized—with the exception of articulation, which is controlled by unilateral motor cortices. We also refer to other chapters for a more detailed overview of non-lateralized brain regions involved in these functions. For all three core sub-processes, we first describe the most important findings with respect to the direction and degree of lateralization, and thereafter summarize speculations on what might drive this lateralization based on the seven possibly influencing factors mentioned earlier. We then discuss the role of the RH, which has a pivotal role in the processing of prosody and metaphors, but also gains importance when language is impaired (e.g., in the case of dyslexia) or extended (e.g., in the case of bilingualism). Finally, the relationship between language lateralization and other asymmetric functions has become a hot topic in research, in line with the shift from individual neural nodes to highly interactive brain networks within and across domains. It will become clear that language lateralization can be a unique gateway to gain knowledge about how the human brain is organized.

Speech Production

In the nineteenth century, Marc Dax attributed speech production to the LH for the first time. Paul Broca published his seminal paper in 1865 stating that we speak with our left hemisphere, after observing a lesion to the third gyrus of the inferior frontal cortex in two severely speech-impaired patients (Broca, 1865; see Wilson, Chapter 2 in this volume). The lesioned region corresponded to what we still call Broca's area today, including the *pars opercularis* (approximately Brodmann area 44) and *pars triangularis* (approximately Brodmann area 45). Despite widely accepted insights that language is much more complex than speaking with Broca's area, activity in this region has long been equalized to language, in particular in the domain of laterality. Clinicians, for example, localize language most often in the LH because many patients are prevented from speaking when the LH is temporarily anesthetized by sodium amytal in the Wada test (Wada & Rasmussen, 1960). The preponderance of the LH in language received even stronger confirmation from research with split-brain patients, also in the 1960s (Gazzaniga, Bogen, & Sperry, 1962). These patients have their corpus callosum and anterior commissure severed in order to isolate intractable epileptic seizures in one hemisphere. They could not name an object held in their left hand, connected to the contralateral RH. This verified that the LH houses speech production, as it could not receive the necessary information via interhemispheric transfer (see Gazzaniga, 1975, 2005, for reviews). Remarkably, these findings were generalized as evidence for overall LH language dominance for decades. This is reflected in laterality assessments of more recent research: Many behavioral and neuroimaging paradigms are compared against outcomes of the Wada test (e.g., Binder et al., 1996; Hirata et al., 2010), or start from production when studying language lateralization, albeit with the notion that their results reflect speech production lateralization and not language lateralization as a whole (e.g., Abbott, Waites, Lillywhite, & Jackson, 2010).

Behaviorally, visual half-field tasks reveal an LH speech dominance when pictures presented in the right visual field are named faster than pictures in the left visual field because the partial crossing of optic fibers at the optic chiasm sends visual information to the contralateral hemisphere. Van der Haegen, Cai, Seurinck, and Brysbaert (2011) presented this behavioral approach as a screening method to identify (a)typically speech-lateralized participants. Their visual half-field picture-naming latencies correlated significantly ($r = 0.65$) with a functional magnetic resonance imaging (fMRI; see Heim & Specht, Chapter 4 in this volume) word-generation task in 50 left-handers with variable directions and degrees of lateralization. Neuroimaging techniques—and in particular fMRI because of its good spatial resolution—are today widely used to map brain regions involved in speech production and their lateralization. The verb-generation task (i.e., saying a verb associated with an object), word-generation task (i.e., generating a word starting with a target letter), and picture naming are most popular for speech-production lateralization. The results are often expressed in indices reflecting the direction and degree of lateralization, in line with the view that lateralization is graded and not absolute (Behrmann & Plaut, 2015), a notion that is not taken into account by the Wada test. The widely used toolbox by Wilke and Lidzba (2007), for example, compares the difference in neural activity between LH and RH homologue areas, thereby giving more weight to voxels activated at a higher activity level to avoid basing the indices on arbitrarily chosen statistical thresholds (see Seghier, 2008, for methodological issues in calculating lateralization indices). Early large-scale studies using word generation in fMRI (Pujol, Deus, Losilla, & Capdevila, 1999) or functional transcranial cerebral Doppler sonography (comparing blood flow velocity in the left and right middle cerebral arteries; Knecht et al., 2000) estimated LH speech dominance to be present in about 95% of right-handers but only 75% of left-handers, boosting the belief that handedness affects language lateralization. Mazoyer et al. (2014) scanned 297 healthy participants balanced for handedness during a sentence production task (i.e., silent sentence generation versus repetition of months of the year as overlearned sequence repetition). Lateralization indices based on individual contrast-activity maps (with most activity in the LH inferior frontal gyrus and lower part of the precentral gyrus, and RH activity at the junction of the middle and inferior temporal gyri in the occipital lobe) divided the participants into typical LH dominants (88% right-handers, 78% left-handers), atypical RH dominants (the remaining 7% left-handers), and participants with bilateral patterns (12% right-handers, 15% left-handers). Overall, these studies agree that the majority of participants produce speech dominantly with their LH, but left-handers have a higher incidence of atypical bilateral or RH dominance.

These laterality studies focused on Broca's area during speech production. Most lateralization indices were based on combined activity in the *pars opercularis* and *triangularis*. It should be noted that Broca is a large region that can be divided into several sub-regions, for example six regions based on neurotransmitter receptor type (Amunts et al., 2010). It is not surprising, then, that it also turns out to be a heterogeneous area at the functional level, linked to semantic processing, syntactic processing, motor functions, music perception and execution, and so on (e.g., Fadiga, Craighero, & D'Ausilio, 2009) apart from phonological processing. It is thus important for researchers to specify on which regions their lateralization estimates were based. Speech production also activates a mosaic of cerebral regions outside Broca's area. Again, even though researchers are aware of this, individual indices should be reported separately for other speech production-related areas if we want to reach a complete image of lateralization. Indeed, the lack of reporting lateralization indices of sub-processes reflects the general duality between psycholinguistics focusing on higher-order level processes (e.g., the *pars opercularis* and *triangularis* for word retrieval) and motor control neuroscientists investigating lower-level articulatory processes (e.g., pre- and post-central motor regions associated with mouth movements; Indefrey, 2011; Price, 2012), as highlighted by Poeppel, Emmorey, Hickok, and Pylkkänen (2012). Broca's area may indeed remain the most important region for speech production, and if all regions co-lateralize, a limitation to the classical *pars opercularis* and *triangularis* may not be problematic, but differences in the degree of lateralization may help explain relationships with other brain regions and possible causes of lateralization, which we will now discuss.

Anatomically, Broca's area has been found to be larger in the LH than RH, but this may mainly apply to Brodmann area 44 (*pars opercularis*). Amunts et al. (1999) divided Broca's area into 10 different regions based on cytoarchitectonic laminar patterns. Despite large between-participant differences, only area 44 showed a clear left asymmetry in all brains. The same authors later reported a significant lateralization of cholinergic M2 receptors in this area (Amunts et al., 2010). The relationship between functional and anatomical asymmetries remains puzzling, however. Keller et al. (2011) compared 15 healthy participants with a functional LH dominance during word generation with 10 RH dominants. Volume asymmetry of the insula could predict 87% LH and 90% RH functional dominance, and the termination of the right posterior Sylvian fissure lay more vertical in LH dominants, but planum temporale volume asymmetry had no predictive value. Even more surprisingly, gray matter asymmetry of Broca's area, considered as the core region activated during word generation, did not correlate with functional asymmetry. Likewise, Greve et al. (2013) found volume asymmetry differences in the insula in 34 LH speech-dominant and 21 RH speech-dominant left-handers identified by Van der Haegen et al. (2011), but not in the *pars opercularis/triangularis* (again, participants were strikingly divided into an LH- and an RH-dominant group based on their functional asymmetry in these regions), nor in the planum temporale or Heschl's gyrus. Exploratory surface-based analysis did find small differences in the posterior temporal gyrus (overlapping with planum temporale) and the ventral occipito-temporal region involved in reading.

Evolution is a second factor that has been related to speech lateralization. It has been theorized that language evolved from manual gestures. The main argument is found in the similar location of Broca's area in humans and the F5-area in monkeys, housing the mirror-neuron system. Mirror-neurons respond to both the execution of manual actions and the perception of the same movements, such as reaching and grasping. This created the possibility to imitate, and from there, more complex movements such as speech articulation could evolve, leading to communication via speech (Rizzolatti & Arbib, 1998). Bipedalism and more complex hand movements in tool use further contributed to the evolution of complex human communication with, for example, syntax (Corballis, 2003; see Vingerhoets et al., 2013, for a correlated lateralization pattern between tool use pantomiming and speech production). It is the vocal mechanism in Broca's area that would have led to unilaterality, as articulation does not require bilateral control, even though this view has not fully been accepted yet because asymmetric speech perception may have evolved first; the vocal tract used for articulation developed in *Homo sapiens* 170,000 years ago, whereas left lateralization of Broca's area was already reported for *Homo habilis* nearly two million years ago (Corballis, 2003). In this light, it would be useful to dissociate sub-regions of Broca involved in manual gestures related to communicative from non-communicative actions.

With respect to development, studies examining the lateralization of speech in young infants are sparse but seem to agree that strong LH frontal lateralization during expressive language (e.g., verb generation, verbal fluency) is already present in children between the ages of 3 and 18 years (e.g., Holland et al., 2007; Paquette et al., 2015; Sowman, Crain, Harrison & Johnson, 2014; see Minagawa & Cristia, Chapter 7 in this volume). Paquette et al. (2015) tested a sample with an age range between 3 and 30 years old with a near-infrared spectroscopy verbal fluency task in which participants had to sum up as many semantic category items as possible. Neural activity bilaterally increased with age in fronto-temporal language regions, but the degree of LH lateralization remained stable from infancy until young adulthood.

Investigating changes in laterality due to increased experience with speech is difficult, given the early use of expressive language in life. Inferior frontal activity has been observed during sign language by deaf participants, with minimal differences compared to normal hearing participants (e.g., Emmorey, Mehta, & Grabowski, 2007, using a positron emission tomography (PET) picture-naming task with face orientation as a control condition), pointing to an amodal expressive language by Broca's area and in line with previously described commonly developed neural networks for speech and gestures. Sign language does evoke more LH parietal activity, such as in the supramarginal gyrus linked to hand configuration and superior parietal lobule associated with proprioceptive monitoring of gestures (Emmorey et al., 2007). Allen, Emmorey, Bruss, and Damasio (2013) observed a larger volume of the *pars triangularis* in deaf signers compared to normal hearing signers and non-signers, along with increased gray matter volume in the visual calcarine sulcus, but no differences in lateralization. These results suggest that deaf signers have increased language areas bilaterally because of their highly demanding language system.

Finally, speech laterality explained by impairment brings us back to where we started this section, namely the observation of Paul Broca that the so-called motor aphasia in his right-handed patients was caused by an LH lesion in the inferior frontal gyrus (Broca, 1865). Later reports estimated aphasia due to unilateral LH lesions to occur in 60% of right-handers and 32% of left-handers, whereas right-hemispheric lesions led to aphasia in only 2% of right-handers but 24% of left-handers (Benson & Geschwind, 1985). Interestingly, the temporal cortices that are considered to contain the second most important areas for language were discovered in a similar way, namely by the observation of so-called sensory aphasia after an LH lesion in Wernicke's area, now known to be important for semantic auditory language processing.

Auditory Speech Processing

About one decade after Paul Broca published his seminal paper describing patients with speech problems as having motor aphasia, the German neurologist Carl Wernicke introduced the so-called sensory aphasia to refer to the syndrome of losing speech comprehension due to a lesion in the LH posterior temporal gyrus (Wernicke, 1874). In laterality research, auditory speech comprehension also seems to be considered as the second most important language sub-process, with speech being more often taken as an equivalent to general language lateralization (see Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume). From an ontogenetic point of view, this is counterintuitive, as speech comprehension develops before speech, already in utero (Partanen et al., 2013). Some researchers do use auditory speech perception as a language laterality measurement, such as in the widely used behavioral dichotic listening task (Kimura, 1961). In this paradigm, participants are presented with auditory stimuli in both ears, often consonant-vowel syllables. The participant is asked to indicate which of two different input stimuli (s)he heard best. Reporting most signals from the right ear is seen as a marker of LH auditory speech dominance because of the preponderance of auditory pathways running from the ear to the contralateral auditory cortex—but note that in the auditory modality, ipsilateral connections are also highly present (Kimura, 1961). Hugdahl et al. (1997) found a right-ear advantage in 92% of right-handers who were LH (speech) dominant in the Wada-test. Tzourio-Mazoyer, Petit, et al. (2010) assessed language dominance, operationalized as story listening in the participants' mother tongue, versus an unknown foreign language in an fMRI study with 94 right-handers. LH asymmetry was found in the posterior superior temporal sulcus, the inferior frontal gyrus, and precentral gyrus, with a reduced lateralization degree in the presence of familial sinistrality, a smaller head size, and absence of strong manual preference.

Auditory speech recognition thus seems to lateralize to the LH. However, studies manipulating different components of speech comprehension point at two pathways. Bozic, Tyler, Ives, Randall, and Marslen-Wilson (2010) found bilateral fronto-temporal activity for the processing of general perceptual complexity and sound-to-meaning conversion during speech comprehension, whereas an LH inferior frontal asymmetry was only found when linguistic morpho-syntactic complexity of the auditory stimuli was increased. Hickok and Poeppel (2007; see also Hickok, Chapter 20 in this volume) described the auditory dual network in more detail. According to their theory, a ventral stream, including middle and posterior temporal cortices, connects acoustic signals to lexical meaning and is hence targeted by speech recognition tasks. In contrast, a dorsal stream running through the superior temporal sulcus bilaterally, a left part of the Sylvian fissure at the border of the parietal and temporal lobe, and left posterior frontal regions translate acoustic signals into articulatory codes and are activated during sublexical tasks such as syllable discrimination. Importantly, the ventral stream is bilaterally represented, which explains why speech comprehension is not necessarily devastated after unilateral damage, but it is the dorsal stream accounting for speech perception that is LH lateralized (Hickok & Poeppel, 2007). In addition to a ventral and dorsal stream, auditory speech processing has been thought to show time-related interhemispheric differences. The LH would be specialized in fast information processing, such as in the case of identifying rapidly changing sounds in speech, and the RH for slower spectral information that is required for prosodic analysis of a speech stream (Zatorre, Belin, & Penhune, 2002). Hickok and Poeppel (2007), in contrast, propose that the ventral stream integrates slow speech information in the RH, but fast information bilaterally (but see Scott & McGettigan, 2013). A review by Specht (2013), however, suggests that a more pronounced LH asymmetry is observed for lexico-semantic compared to auditory-phonetic processing and from posterior to anterior regions involved in speech processing showing that it is still under debate which aspects of speech processing are lateralized.

Comparing the degree of lateralization for speech production and comprehension might provide further insights, given their close functional relationship, especially in the dorsal stream. Tzourio-Mazoyer, Josse, Crivello, and Mazoyer (2004) found stronger functional asymmetries for production (verb generation) than comprehension (story listening, both against rest) in a PET study. The weaker asymmetry during speech comprehension was mainly driven by the superior temporal gyri and Heschl's gyri. On the other hand, Häberling, Steinemann, and Corballis (2016) recently found no significant difference between three lateralization indices based on activity in the inferior frontal gyrus during verbal fluency word generation (against fixation) and the inferior frontal gyrus and middle/superior temporal gyrus during a synonym judgment comprehension task (against similarity of letter strings). It may be that the importance of lexico-semantic information in the visual synonym task boosted left lateralization, which again highlights that a variety of paradigms and especially control conditions can lead to different outcomes. Häberling et al. conclude that it makes sense for the fronto-temporal regions to tune their lateralization in order to optimize information exchange, and that the left lateralization of the dorsal stream introduced by Hickok and Poeppel (2007) uniquely adapted to vocalization in humans.

In sum, auditory speech processing is at least partly LH lateralized, but future research needs to clarify exactly which aspects are specialized to one hemisphere and whether this specialization is less extremely pronounced than speech production. We will now discuss studies providing information on the possible factors affecting laterality. First, Häberling et al. (2016) included an overrepresentation of left-handers to ensure sufficient variability in the lateralization indices and indeed found less asymmetry in this group. Van der Haegen, Westerhausen, Hugdahl, and Brysbaert (2013) pursued the left-handed approach more extremely and compared their atypically RH speech production lateralized left-handers (based on an fMRI verbal fluency word-generation task) with LH dominant left- and right-handers in a behavioral dichotic listening task. At the group level, RH speech dominants indeed turned out to have a left-ear advantage, whereas LH speech dominants had the expected right-ear advantage. At the individual level, however, the dichotic listening task showed variability in all groups. This can be due to more variability in a behavioral task, or an indication that speech perception in the case of syllable discrimination is more symmetric than speech production (Hickok & Poeppel, 2007). No effects of handedness were found when left-handers were considered as a homogenous group, which suggests the importance of their individual differences in hemispheric speech lateralization.

Evolutionary speculations on the development of auditory perception and comprehension go along with anatomical asymmetries. The planum temporale around the superior temporal gyrus, involved in imagining and hearing sounds (Price, 2012), is larger in the LH in humans (Geschwind & Levitsky, 1968) as well as chimpanzees (Hopkins, Marino, Rilling, & MacGregor, 1998), but not in rhesus monkeys and baboons (Wada, Clarke, & Hamm, 1975). These results point to the importance of leftward asymmetries in the planum temporale, which might be linked with some communicative functions (Corballis, 2009; Hopkins & Nir, 2010). Familial sinistrality affected the planum temporale in Tzourio-Mazoyer, Simon, et al. (2010): Having a left-handed relative decreased the surface size of the area by 10% and led to a larger gray matter volume, accompanied by a smaller leftward asymmetry. The size and gyrification pattern of Heschl's gyrus (belonging to the bilateral superior temporal gyri and involved in speech and non-speech sound processing; Price, 2012) also seems to play a role in establishing language lateralization. Marie et al. (2015) observed less duplications of Heschl's gyrus in the RH and a decreased LH asymmetry of the anterior gyrus of Heschl in left-handers. Tzourio-Mazoyer et al. (2014) linked the duplication and decrease in anatomical surface area of the anterior gyrus to a decrease in functional asymmetry in Heschl's gyrus during word-list listening. Leroy et al. (2015) reported a superior temporal asymmetrical pit that may be unique to humans, that is, more LH sulcal interruptions in a superior temporal sulcus region ventral to Heschl's gyrus, leading to a deeper structure in 95% of humans. This may be a precursor of human language lateralization as the asymmetry is present in healthy adults as well as infants, (a)typically lateralized speech dominants, left- and right-handers, and participants with *situs inversus*, autism spectrum disorder, Turner syndrome, or corpus callosum agenesis, but not in chimpanzees. A final anatomical asymmetry is found in the long-distance tracts of the arcuate fasciculus, connecting frontal and temporoparietal language areas such as Broca's area and Wernicke's, respectively. Its direct pathway (apart from the indirect pathway via the inferior parietal cortex) is LH lateralized in more than 80% of healthy participants (Catani et al., 2007). The structural asymmetry, however, seems to be independent from handedness and functional language lateralization as measured with a verbal fluency verb-generation task against tone listening (Vernooij et al., 2007). The recent diffusion tensor imaging study by Allendorfer et al. (2016) similarly reported no asymmetry differences for the pathway between left- and right-handers, even though left-handers as a group were less extremely LH lateralized in the functional verb-generation task. In contrast, Ocklenburg, Schlaffke, Hugdahl, and Westerhausen (2014) did find positive correlations between tract volume and fractional anisotropy of the LH arcuate fasciculus with the degree of right-ear advantage in a dichotic listening task.

Apart from evolutionary and anatomical insights, genetic studies are slowly adding information. With respect to speech perception, Ocklenburg et al. (2013) linked two polymorphisms of the *FOXP2* gene, rs2396753 and rs12533005, to the right-ear advantage in a dichotic listening task presenting consonant-vowel syllables to about 450 healthy participants. Variations in the *FOXP2* gene, however, also have been associated with language functions other than speech perception (e.g., reading ability; see discussion later in the chapter), and dichotic listening activates many brain regions such as the superior and middle temporal gyrus, pre- and post-central gyrus, supplementary motor area, and middle and superior frontal gyrus (Van den Noort, Specht, Rimol, Ersland, & Hughdahl, 2008). As mentioned by the authors themselves, it remains unclear how exactly molecular changes affect speech processing laterality.

Further, changes in auditory speech lateralization have been observed during development. Perani et al. (2011) found that perisylvian language areas in the inferior frontal and superior temporal cortices are already activated by 2-day-old babies listening to speech, but the auditory cortex showed RH dominance. LH speech perception was present in 3-month-old infants (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002), accompanied by a structural LH asymmetry of the arcuate fasciculus (Dubois et al., 2009). Another important difference compared to the adult language network pointed out by Perani et al. (2011) was the functional connectivity: Whereas most adults' fronto-temporal connections are strongest within the LH, 2-day-old babies mainly activated interhemispheric connections between LH and RH temporal regions. This preponderance of interhemispheric connectivity is still present by the age of 6 years (Friederici, Brauer, & Lohmann, 2011).

In deaf people (see also, in this volume, Newman, Chapter 14, and Corina & Lawyer, Chapter 16), the superior temporal gyrus reacts on visual motion stimuli and is more strongly connected to the calcarine fissure. This functional connectivity is positively correlated with the duration of wearing a hearing aid in hearing-impaired participants (Shiell, Shampoux, & Zatorre, 2014). With respect to the lateralization of a reorganized auditory cortex after unilateral deafness, Van der Haegen et al. (2016) found no difference in LH dominance for right-sided deaf participants who had profound hearing loss from birth during a semantic speech-listening task (i.e., judging whether or not a heard sentence refers to an animal against noise).

READING

Reading (see Paz-Alonso, Oliver, Quiñones, & Carreiras, Chapter 24 in this volume), the third main subprocess of language, developed much later than speech production and comprehension in evolution. It originated about 6,000 years ago, even though being able to read was still rare only a century ago. Reading also develops last at the individual level, after extensive learning via instruction.

A region in the LH ventral occipito-temporal (vOT) sulcus has been identified as a crucial area and was consequently called the "visual word form area" (Cohen et al., 2000). Dehaene and colleagues argue that the area became specialized in a way of neuronal "recycling" (i.e., neurons were tuned to recognize visual words, but this evolved in an existing framework that was not genetically manipulated by learning to read). Plasticity could only occur within the existing constraints of the brain, and reading evokes most neural activity in the ventral visual cortex because of the close relationship to recognition of line junctions that form objects (see, e.g., Dehaene & Cohen, 2011, for a review). This area has, however, been shown to be activated by nonvisual stimuli as well, and interacts with top-down information coming from frontal phonological areas (Price & Devlin, 2011). The latter is especially interesting in light of lateralization. Seghier and Price (2011) found that the LH dominance of the vOT relative to pictures varied across three sub-regions of the area, mainly driven by decreased activity in the RH. Laterality indices of the posterior vOT were mostly influenced by RH reduction for letters and words relative to objects and nonobjects, indicating that this sub-region is related to visual attributes. The anterior vOT, on the other hand, was more activated by familiar (words and objects) than unfamiliar (Greek letters and nonobjects) stimuli and by a semantic task rather than reading aloud, suggesting that the lateralization of the anterior vOT is influenced by connections with frontal phonological and semantic regions. The middle vOT was affected by a mixture of visual and nonvisual factors. Inferior frontal regions already play a role in very early stages of visual word recognition. Cornelissen et al. (2009) did not find a significant time difference between the peak of the inferior frontal gyrus (after 130 ms) and the visual mid-fusiform gyrus (after 140 ms) in a passive word-viewing task. Words further elicited activity in the anterior and left posterior middle temporal gyrus, left superior temporal gyrus, and angular and supramarginal gyri. Co-lateralization of the inferior frontal gyrus during word generation and vOT during lexical decision was also found in left-handers with typical LH and atypical RH dominance (Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2008; Cai, Paulignan, Brysbaert, Ibarrola, & Nazir 2010; Van der Haegen, Cai, & Brysbaert, 2012). Pinel et al. (2014) compared reading (words versus scrambled stimuli) and auditory speech (native language sentences versus tone listening) lateralization in a one-back task. Participants with the strong leftward asymmetry in the middle superior temporal sulcus during speech processing also had a stronger LH lateralized vOT, driven by reduced RH activity, as in Seghier and Price (2011). These findings together reveal an influence from earlier developed functions such as speech production and comprehension on the recently developed reading skill. The vOT remains the most investigated region involved in visual word recognition, but it is clear that reading, as all cognitive functions, functionally relies upon a broader network, including frontal and temporal regions to support phonological and semantic processing. Richardson, Seghier, Leff, Thomas, and Price (2011) presented three possible reading routes connecting the posterior inferior occipital, posterior superior temporal gyrus, anterior superior temporal sulcus, and vOT region, with one pathway even running through the first three regions without involvement of the vOT. To our knowledge, no laterality differences have been reported for these routes.

Returning to our seven possible factors influencing laterality, we will now discuss evolutionary theories further than the previously mentioned neuronal recycling view, as reading is too recent and too unique for humans to speculate on parallel development of brain regions with nonhuman primates. Anatomically, two white-matter tracts end near the vOT: the inferior fronto-occipito fasciculus and the inferior longitudinal fasciculus running from the occipital lobe to anterior and medial temporal lobe. A third fasciculus, the vertical occipital fasciculus, runs from the lateral occipito-temporal sulcus to lateral occipital and inferior parietal lobes (Yeatman, Rauschecker, & Wandell, 2013; see Catani & Forkel, Chapter 9 in this volume). Again, different asymmetries of these pathways related to atypical (functional) lateralization have not yet been reported, to our knowledge. The only significant difference found was the more leftward/rightward gray matter volume asymmetry for speech LH and RH dominants, respectively, in Greve et al. (2013).

Pinel et al. (2012) scanned 94 healthy participants while they silently read sentences and linked the two single-nucleotide polymorphisms rs6980093 and rs7799109 in the *FOXP2* gene (associated with language impairment) to their functional LH lateralization of the frontal cortex, and rs17243157 variants in the *KIAA0319/TTRAP/THEM2* gene (associated with reading disabilities) to reduced LH asymmetry in the superior temporal sulcus. Other genetic influences on the lateralization of the vOT were found in Pinel et al. (2014), who tested monozygotic and dizygotic twins during their one-back visual task. Monozygotic twins showed intra-pair correlations as high as intra-participant correlations measuring replicability for LH vOT activity. The number of voxels activated above a $t > 1$ threshold was also more similar between monozygotic than dizygotic twins, suggesting that LH vOT activity is at least partly driven by genetic influences. This may be contradictory to the evolutionarily recent acquirement of the reading skill, but Pinel and colleagues conclude that this can be explained by the neural constraints in which the reading circuit developed. Genetic underpinnings of properties of the visual cortex to be able to recognize detailed information in central vision and connections to frontal and temporal regions may drive the heritability of the LH vOT activity.

To explore how the vOT evolves during learning to read in education, Ben-Shachar, Dougherty, Deutsch, and Wandell (2011) scanned children aged 7–12 four times in one year during an implicit reading task: Children were asked to indicate the color of a fixation mark that was presented together with word stimuli varying on visibility at four levels. Sensitivity to the word visibility was linked with better performance of overt speed reading and increased with age, especially in the LH posterior occipito-temporal sulcus nearby the vOT. The occipital V1 and posterior parietal cortex did not show such correlation, and remarkably neither did the RH occipito-temporal reading region. Thus, for developing perceptual expertise of words in a noisy context, the LH seems to play a more important role than the RH homologue area.

Dehaene, Cohen, Morais, and Kolinsky (2015) review how gaining reading experience by illiterates changes neural circuits. Not only letters, but also objects and faces, are better discriminated when acquiring reading, as reflected in an increase of activity in the early bilateral occipital regions (Dehaene et al., 2010). Moreover, the ventral visual pathway, including the vOT, becomes specialized for the script that is being trained, with a positive correlation between the amount of neural activity and reading speed (Dehaene et al., 2010). Learning an artificial language can even change the brain after a short training: Xue, Chen, Jing and Dong (2006) conducted two weeks of visual training and two weeks of phonological and semantic training with normal readers. Visual training decreased activity bilaterally in the fusiform cortex and LH inferior occipital cortex, whereas phonological training had the opposite effect. Semantic training affected the RH fusiform area more. Reading acquisition further improves the processing of phonological representations; the vOT is activated by phonology only in literates (Dehaene et al., 2015). Perhaps the most striking change in terms of laterality is the influence that reading experience has on the lateralization of non-reading-related face recognition. The fusiform face area specialized for faces in the ventral visual cortex is reduced in the LH but enhanced in the RH when literacy increases (Dehaene et al., 2015). We will discuss the remarkable relationship between the laterality of word and face recognition in more detail in the following section.

Finally, reading impairment has been associated with differences in laterality. A meta-analysis of functional connectivity in dyslexic and control participants pointed at weaker LH connections between regions involved in visual and visuo-phonological processes, such as the LH inferotemporal region, fusiform gyri, inferior frontal, premotor and supramarginal cortices. In addition, dyslexics activated a dorsal fronto-parietal network less, including LH parietal and premotor cortices, associated with altered motor and visuospatial attention (Paulesu, Danelli, & Berlingeri, 2014). Diffusion tensor imaging (see Catani & Forkel, Chapter 9 in this volume) studies generally found lower fractional anisotropy in white-matter tracts running through temporoparietal and frontal regions, especially in the LH arcuate fasciculus and corona radiata. Ventral tracts related to reading, such as the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, were less affected (see Vandermosten, Boets, Wouters & Ghesquière, 2012, for a review).

THE ROLE OF THE RIGHT HEMISPHERE IN LANGUAGE PROCESSING

In contrast to the widely studied core sub-processes discussed earlier, the role of the RH receives much less attention in neuroscientific research. It is well-known, though, that the RH is active in several ways: (1) It plays a dominant role in some sub-processes such as prosody and metaphor comprehension (see, in this volume, Rapp, Chapter 28, and van Berkum, Chapter 29). (2) Neuroimaging has made clear that language lateralization in all functions is not absolute, processes are distributed across the hemisphere with a dominance in the LH for most language processes, and the RH can even be the dominant hemisphere in atypical left-handers. Moreover, individual differences are often explained by variations in RH activation. (3) Language impairments and mental disorders with a language component often increase the importance of the RH, as well as an extension of the language system, such as in the case of bilingualism. We will now discuss these three domains in more detail.

Prosody refers to either the variations in pitch and rhythm that form the emotional expression of the speaker, called emotional prosody, or the stress within sentences and words, called linguistic prosody. A meta-analysis by Belyk and Brown (2014) makes clear that the two types of prosody share many common brain regions, but are nevertheless distinct and differ in their lateralization. Pitch modulation is a common factor of both prosody types, leading to joint activation in the posterior superior temporal gyrus, with an RH dominance for emotional prosody and a more bilateral distribution for linguistic prosody. Common activity was also found in the RH supplementary motor area linked to speech production. A differentiation was found in the inferior frontal gyrus: evaluating affective cues in speech activates the pars orbitalis bilaterally (Brodmann area 47), a region connected to areas involved in experiencing and perceiving emotions, such as the amygdala, whereas linguistic prosody is more related with the bilateral pars opercularis (Brodmann area 44), which can be explained by its role in lexico-syntactic processing (Belyk & Brown, 2014). These meta-analytic results thus suggest RH involvement of auditory temporal regions and bilateral involvement of frontal regions irrespective of prosody type, in contrast to inconsistencies regarding lateralization in individual neuroimaging studies. For example, Witteman et al. (2014) found a right-ear advantage for both emotional and linguistic evaluation of dichotic listening stimuli associated with an early negativity event-related potential latency (see Leckey & Federmeier, Chapter 3 in this volume) in the contralateral hemisphere. In contrast, Wildgruber et al. (2005) did find functional asymmetries in an fMRI experiment in which participants were asked to either judge the emotions (basic emotions: anger, happiness, sadness, fear, and disgust) or linguistic content (i.e., reporting the first vowel following the first heard /a/) of sentences. Apart from common widespread bilateral activation, emotional judgment tapped into an RH network, including the posterior superior temporal sulcus, and dorsolateral and orbitobasal frontal cortices. The linguistic task made use of LH speech areas, such as the dorsolateral frontal cortex. These studies show a less consistent pattern than suggested in Belyk and Brown (2014), which could in part be explained by the different paradigms used.

A similar controversy of RH involvement probably depending on the type of task being used can be found in the literature on non-literal language comprehension, such as metaphor processing. Here again, the fronto-temporal language network is important with LH involvement in inferior, middle, and superior temporal gyri and the inferior frontal gyrus. Yang, Edens, Simpson, and Krawczyk (2009) reported that the amount of RH involvement mainly depends on the difficulty level of the sentences used, and not whether participants have to judge novel or known metaphors. Semantic judgments rely more on frontal areas, whereas imageability affected parietal regions such as the precuneus, but the laterality of these regions depended on the difficulty level of the stimuli.

This leads to the assumption that RH variations can generally explain individual differences in language laterality. Vigneau et al. (2011) evaluated the role of the RH in language tasks in a meta-analysis showing that LH activity occurred much more often in a unilateral fashion, whereas most RH peaks were observed in the case of bilateral peaks (i.e., in combination with LH activity in a homologue region). Phonological tasks activated RH auditory and motor areas (with the exception of only LH mouth-related activity and verbal working-memory tasks). Lexico-semantic tasks made use of RH frontal regions to support attentional and working-memory processes. During high-level sentence and text processing, the RH even had an exclusive role in temporal regions. Seghier, Kherif, Josse, and Price (2011) in addition highlighted that laterality differs across regions, confirming our general claim that language laterality should not be expressed in one unitary lateralization index. In Seghier et al. (2011), high LH angular gyrus activity was connected with low LH ventral precentral laterality. Even more interesting, interregional and inter-participant variability across 50 activated brain regions and 82 healthy participants performing a semantic word-matching task was mainly driven by differences in RH rather than LH activation. A dynamic causal modeling analysis of data from the same task revealed that the degree of LH laterality during word matching increased when the coupling from LH to RH dorsal frontal cortices decreased (Seghier, Josse, Leff, & Price, 2011).

If RH activity determines individual laterality patterns, can it also predict differences in performance? Van Ettinger-Veenstra et al. (2010) ran a dichotic listening task (taken as a general language laterality measure) and fMRI sentence completion task (i.e., complete the last word of a sentence versus the same sentences with asterisks replacing letters) to correlate their lateralization indices with performance on a wide variety of language tasks (e.g., sentence, text and metaphor comprehension, picture naming, and verbal fluency). Verbal fluency correlated positively with right-ear reports during dichotic listening, but overall, a decreased right-ear advantage led to better performance in almost all language assessment tasks. Rightward fMRI indices were also associated with better reading ability in the posterior temporal lobe and better comprehension scores in the inferior frontal cortex. On the other hand, Prat, Mason, and Just (2010) found increased RH frontal, temporal, and inferior occipital activity in participants with a smaller vocabulary size when they had to read more complex sentence pairs. This suggests that the RH is activated more if the participant experiences difficulties in language comprehension. Dehaene et al. (2010) reported increasing LH activity in the vOT with increasing literacy. Pinel et al. (2014) localized the vOT more anteriorly (associated with larger orthographic units) in participants who showed a smaller difference in reaction time when reading pseudo-words compared to words, but did not find differences in the amount of activity. Related to reading impairment, dyslexia was associated with less optimal connections between language areas in the LH only (Paulesu et al., 2014; Vandermosten et al., 2012). The different paradigms again impede straightforward conclusions about the relationship between the degree and direction of laterality, on the one hand, and language performance, on the other hand. Moreover, the functions tested in behavioral performance assessments are often different from those used to calculate the functional neural lateralization indices (see also Boles & Barth, 2011). One could speculate that, for example, RH activity increases when phonological, semantic, or reading processes become too difficult for the LH alone, and that language becomes more LH lateralized when performance increases because the RH is no longer needed. A similar idea was formulated by Prat et al. (2010) as the RH spillover hypothesis: that is, the RH contains coarser language abilities than the LH, but can take over if needed, for example, after a lesion or when the LH exceeds its capability during difficult tasks.

The dynamic role of the RH can be studied when existing knowledge is extended by learning a new language (see Green & Kroll, Chapter 11 in this volume). Xiang et al. (2015) collected longitudinal diffusion tension imaging data from native German speakers following an intensive six-week Dutch course. They found that tracts between Brodmann area 6 and temporal regions, overlapping with the arcuate fasciculus, became more RH lateralized in the beginning stages of the course but again turned into an LH dominance with better proficiency in their second language. It thus seems that structural connectivity is indeed reorganized to the RH when bilingualism challenges the language network, but then again becomes typically LH dominant when proficiency is high enough. In line with this point of view, Kepinska et al. (2017) also pointed out that fronto-parietal structural connectivity (right anterior segment of arcuate fasciculus) in the right hemisphere plays an important role in superior language learning, which might involve attentional processes and reasoning abilities. A functional increase has also been observed for bilinguals relative to monolinguals during native language picture naming and reading aloud in the LH dorsal precentral gyrus, *pars opercularis/triangularis*, superior temporal gyrus, and planum temporale (Parker Jones et al., 2012). Parker Jones and colleagues attributed this difference to a higher demand of word retrieval, articulation, and speech monitoring in bilinguals. A meta-analysis of behavioral lateralization tasks by Hull and Vaid (2007) pointed to the importance of taking age of acquisition into account: Early bilinguals who learned their second language before the age of 6 activated language areas more bilaterally, whereas later bilinguals were more LH dominant, especially when proficiency was low, English was the second language, and laterality was measured in a dichotic listening task. Learning a new language even influences brain areas recruited during native-language processing. Mei et al. (2014) trained Chinese speakers who had English as their second language with an artificial language based on Korean Hangul characters. The training focused on semantic learning, not just on acquiring visual-phonological correspondences. The results showed reduced LH activity in the *pars opercularis/triangularis*, and bilateral inferior temporal gyrus, fusiform gyrus, and inferior occipital gyrus while reading Chinese. The semantic training even influenced similar regions during English reading. In line with Xiang et al. (2015), the effects were strongest in the initial stages of the training and decreased with increasing proficiency. Finally, laterality differences in bilingualism depend on the similarity between the two acquired languages, usually tested in bilinguals with knowledge of alphabetical languages such as English and logographic languages such as Chinese and Japanese Kanji. English-Chinese bilinguals activate the RH posterior fusiform cortex more than English monolinguals, in a similar way as Chinese monolinguals show a more rightward lateralization during reading than English monolinguals (Mei et al., 2015). Koyama et al. (2014) drew similar conclusions from late bilinguals who were either native speakers of Japanese syllabic Kana and logographic Kanji languages and learned English, or native English speakers who mastered Japanese. A visual one-back reading task revealed less LH lateralization in the posterior lateral occipital region for logographic Kanji compared to syllabic Kana and alphabetic English, irrespective of the participant's first language. If the first and second language were non-logographic, no lateralization differences were found.

Finally, more RH activity has been associated with language-related areas in mental disorders. *FOXP2* polymorphisms, previously linked to reduced reading ability and dyslexia, were also associated with schizophrenia and autism spectrum disorder (Gong et al., 2004; Li et al., 2013). Schizophrenia patients in Bleich-Cohen et al. (2012) showed a reduced LH asymmetry and interhemispheric connectivity in the inferior frontal gyrus, an effect that was more pronounced with increasing severity of negative symptoms. Kleinhans, Müller, Cohen, and Courchesne (2008) found increased activity in RH frontal and superior temporal regions during verbal fluency word generation in participants with autism spectrum disorder, characterized by impairments in speech, syntax, and pragmatic knowledge compared to controls (see also Lindell & Hudry, 2013, for a review concluding that asymmetries become more atypical with increasing language impairments).

Language Laterality in Relation to Other Functions

It is clear from what we have discussed so far that all sub-processes of language can vary in their lateralization across individuals. This can be a fruitful starting point to gain knowledge about how the human brain is organized, both with respect to language and non-language functions (Cai & Van der Haegen, 2015). There are two dominant views on how functions are distributed across the RH or LH. The statistical independence view states that functions develop irrespective of how already established functions are organized. Alternatively, according to the competitive complementary hypothesis, cortical space is limited, and thus brain functions compete with each other for resources. The latter view makes clear that apart from the seven possible influences on laterality we reviewed per language sub-process (handedness, anatomy, evolution, genetics, development, experience, and impairment) there is an eighth possible factor: cooperative and competitive non-language functions (Behrmann & Plaut, 2013). Recent neuroimaging studies most extensively explored the relationship between reading and face recognition, and between speech production and visuospatial attention.

Behrmann and Plaut (2013) introduce three views on brain functioning: (1) the one-to-one vision in which one structure can be coupled with one cognitive function and vice versa; (2) the one-to-many vision in which a cognitive function triggers a network of structures and vice versa; (3) the many-to-many vision that integrates the first two perspectives and argues that structures and functions form distributed but interacting networks. Evidence for the many-to-many view can be found in the ventral visual cortex, where nodes are optimized for a specific visual category such as the vOT for words (Cohen et al., 2000) and the fusiform face area for faces (FFA; Kanwisher, McDermott, & Chun, 1997). At first sight, words and faces have more differences than commonalities. They both contain detailed information that has to be processed in central vision, but face recognition developed much earlier in evolution than reading and consists of coarser elements than the fine-grained line junctions in letters (Behrmann & Plaut, 2013). Statistical independence could argue that spatial frequencies pushed reading into the LH and faces into the RH, with the LH/RH being inherently more sensitive to high/low spatial frequencies, respectively (see Woodhead, Wise, Sereno, & Leech, 2011, who reported interhemispheric sensitivity to spatial frequencies; but see Ossowski & Behrmann, 2015, for evidence that LH high spatial frequency sensitivity was not found in pre-literate children, suggesting that the sensitivity is a consequence rather than cause of reading). Yet, interactions between reading and face recognition have been reported in several recent studies supporting the competitive hypothesis (Dehaene et al., 2010; Dundas, Plaut, & Behrmann, 2013, 2015; Cantlon, Pinel, Dehaene, & Pelphrey, 2011; Li et al., 2013). For example, Dundas et al. (2013) found a right/left visual field advantage for words and faces, respectively, but only in adults and not in children or adolescents. The younger participants showed only a right field advantage for words, with no visual field preference for faces. Face lateralization additionally correlated with reading performance. This could be explained from a developmental point of view that face recognition is bilaterally processed at first, but is then pushed into an RH dominance because words occupy overlapping neurons in the LH in order to optimize the connections with earlier LH lateralized fronto-temporal language regions (Dundas et al., 2013). Cantlon et al. (2011) found an LH occipito-temporal sensitivity to letters and digits, and an RH mid-fusiform dominance for faces in 4-year-old children in an fMRI study showing pictures of these visual categories and shoes. The early RH face dominance somewhat contradicts Dundas et al. (2013), who did not find a face lateralization before the mean adult age of 21, but more interestingly, Cantlon et al. (2011) add evidence for a competing view on word and face processing because children's behavioral symbol (i.e., letters and numbers together) matching scores correlated negatively with face-selective activity in the LH occipito-temporal region, whereas there was not even a correlation found with symbol neural activity itself in the same region. Similarly, behavioral face-matching accuracy was not associated with increased neural sensitivity for faces in the RH face-selective fusiform area, but with decreased activity for shoes, with no association with neural activity for symbols. Thus, visual areas generally seem to specialize by means of pruning away non-preferred categories, rather than favoring preferred categories. With respect to word and face lateralization in particular, an anti-correlation was found in the LH but not in the RH, even though the authors remark that this could be different in other stages of development. Looking at what atypical handedness could tell about this issue, no study to date has compared word and face lateralization in left-handers whose reading lateralization was clearly RH dominant, but Willems, Peelen, and Hagoort (2009) and Bukowski, Dricot, Hanseeuw, and Rossion (2013) found overall reduced RH face lateralization in the FFA of left-handers compared to right-handers. Dundas et al. (2015) confirmed this finding, together with LH word discrimination superiority for both right- and left-handers. In their study, more negative LH N170 event-related potential components (previously shown to distinguish orthographic from non-orthographic stimuli in the LH and sensitive to faces in the RH) during word presentations predicted a stronger amplitude for the N170 for faces and more RH behavioral asymmetries for faces. In the earlier discussed study by Pinel et al. (2014) using a one-back visual task with words and faces, among other visual categories and a speech-processing paradigm, different contributing factors to reading and face lateralization came forward: vOT activity showed significant intra-pair correlations for monozygotic twins but the FFA did not, suggesting that the vOT partially develops under genetic influences, whereas the FFA is more sensitive to environmental factors. RH FFA lateralization did not directly correlate with LH vOT lateralization, but was related to LH lateralization of the superior temporal sulcus during speech listening and reading skill, as operationalized by the additional time cost in naming pseudo-words compared to words. Finally, Badzakova-Trajkov, Häberling, Roberts, and Corballis (2010) confirmed the correlation between RH face recognition and LH word generation, but were among the first to relate these two lateralized functions to another widely studied RH-dominant cognitive function: visuo-spatial attention.

According to Kosslyn (1987), visual attention to stimuli in the environment, like speech production, is unilaterally processed because rapid and precise actions are best coordinated by one control system. In addition, the control systems are best located in opposite hemispheres so that they do not interfere. This is in line with the competitive view in which functions can be crowded out, and in contrast with the statistical independence view in which lateralization of functions develop independently from each other. The 155 participants from Badzakova-Trajkov et al. (2010) did show a small but significant negative correlation between the verbal fluency word-generation task in frontal areas and the bisection task measuring visuospatial attention (i.e., judging whether a vertical line bisects a horizontal line versus indicating whether a vertical line is present in the control condition) in parietal areas. The bisection task was, however, the only task that did not elicit more atypical patterns in left-handers, and its lateralization did not correlate with RH face lateralization. We have argued before that an effect of handedness is not necessary to observe (a)typical lateralization patterns, and visuospatial attention has theoretically not been linked to face processing, but the relationship between speech production and visuospatial attention is indeed more mixed in the literature than the complementary lateralization patterns of reading and face recognition.

The first doubts about causal complementarity came from patient observations with a unilateral brain lesion. If speech and visuospatial attention indeed crowd each other out, then LH-damaged patients should have aphasia with spatial ability problems, and vice versa for RH-lesioned patients (Bryden, Hécaen, & DeAgostini, 1983). This, however, was not always the case: LH lesions led to aphasia, but also to spatial ability deficits or both, with a comparable picture for RH lesions. Zago et al. (2016) also found independence between lateralization indices of speech production (measured by contrasting sentence production based on a line drawing versus recalling the months of the year) and visuospatial attention (measured by line bisection versus fixation). At the group level, the 293 participants balanced for handedness mostly activated LH fronto-temporal language regions during speech production and RH frontal and posterior occipito-parietal-temporal regions during visuospatial attention, but a negative correlation was only found for left-handers with a strong manual preference. A clear interhemispheric distinction was reported by Cai, Van der Haegen, and Brysbaert (2013): All but one of 16 left-handers who were clearly LH lateralized for speech production (i.e., verbal fluency word generation versus nonword repetition) were RH lateralized for visuospatial attention (i.e., line bisection versus indicating whether a vertical line touched a horizontal line), and all 13 left-handers with clear RH speech dominance were LH dominant for visuospatial attention that elicited activation in the dorsal fronto-parietal attention pathway and inferior frontal regions.

Why is there agreement that reading and face recognition negatively correlate in line with a causal complementary view on brain functions, whereas speech production and visuospatial attention only seem to lateralize to the opposite hemisphere in extreme left-handers but support statistical independence in the remainder of the population? It could be that visuospatial attention tasks evoke less stable neural patterns than, for example, the verbal fluency task. Pernet et al. (2016) evaluated the between- and within-subject variance of a speech-production (verb generation triggering Broca's area) and landmark task (indicating which of two lines are smaller or larger, activating the intraparietal cortex) in order to estimate their reliability as clinical presurgical tools. A reliable paradigm should have higher consistency over two sessions tested within the same participant than at the group level, which was the case for word repetition but not for the landmark task. Another possible explanation for a stronger causal complementarity between reading and faces than between speech production and visuospatial attention is that the interplay between the function pairs is based on different underlying mechanisms. In the first pair, faces are presumably crowded out of the LH once the visual cortex needs to adapt to reading, which is preferably dominated by the LH to co-lateralize with earlier developed fronto-temporal language functions (Behrmann & Plaut, 2013). This is a competition for cortical space in homologue areas between an already established and newly developing cognitive function. Language and visuospatial attention, on the other hand, are more widespread throughout the cortex and are presumably separated because they each need a unilateral control system (Kosslyn, 1983). Petit et al. (2015) suggested another evolutionary explanation: In the sample studied by Zago et al. (2016), the dorso-parietal attention network was especially RH lateralized in strong left-handers, and even more so if they were right-eye sighted. Petit et al. argue that processing visuospatial control of the environment in the same hemisphere as their dominant hand may give these left-handers an advantage in, for example, interactive sports. It may thus be that visuospatial attention evolutionarily first lateralized to the RH because of functional advantages, and that language was then crowded out to the LH without having large overlapping neural populations that have to move for a competing function. Whatever reasons future studies will point out with respect to competitive or statistical independent relationships between functions, this overview makes clear that lateralization research, and in particular studies including atypically lateralized left-handers, can reveal interesting insights into brain mechanisms in general.

CONCLUSION

We can conclude from this chapter that language laterality gives unique information on how language and non-language functions are being processed in the human brain. It can be seen (前面刚用了 this overview made clear) that most language functions, such as speech production, auditory speech processing, and reading are dominantly processed in the LH in most humans, even though the degree of laterality can differ across functions and across individuals. Left-handers introduce more variability in the samples studied, leading to insights into mutual interactions when one factor such as speech production is atypically lateralized. Possible causes of an LH dominance have been proposed for each sub-process from studies reporting anatomical, evolutionary, genetic, developmental, experiential factors, and consequences of impaired functions and lesion studies in patients. We further discussed that the role of the RH within language remains underestimated, but prosody and metaphors are well-known to be dominated by the RH in most participants, and its importance to explain individual variability in healthy participants, dyslexia, and mental disorders such as autism spectrum disorder and schizophrenia is widely acknowledged. Recent laterality literature is dominated by neuroimaging studies mapping the direction and degree of lateralized functions, often (but far from always) reporting results of behavioral correlates that make it still unclear to what extent the lateralization of functions affects cognitive performance. It will thus be important to continue to combine different methodologies, while trying to optimize paradigms in order to facilitate the comparability across studies. Finally, language lateralization can be an ideal starting point to explore general brain mechanisms. We have discussed competitive complementarity between reading and face recognition, and, at least in strong or atypically lateralized left-handers, between speech production and visuospatial attention. From a wider perspective, future laterality studies can also reveal how the human brain works, beyond focusing on one or two cognitive functions. For example, Liu, Stufflebeam, Sepulcre, Hedden, and Buckner (2009) identified four asymmetric networks during resting state activity that could roughly be related to regions involved in vision, internal thought, attention, and language. If these networks are indeed independent, with their own degree of inter-individual variability, then neuroscientists should not try to find one explanation (competitive complementarity or statistical independence) for the whole brain, but instead should investigate how and why separate clusters are grouped into networks underlying different functions, and how they are related to each other. One view on how the numerous and complex functions our brain houses can function so well together was given by Fedorenko and Thompson-Schill (2014). They argue that apart from a domain-general attention-related multiple demand network, the language network consists of functionally specialized core regions (i.e., regions that are consistently activated during language tasks and co-activate) and nonspecialized periphery regions (i.e., regions that are activated during language tasks, but can also co-activate with regions belonging to another specialized network depending on the current task). In this chapter, we have mainly focused on the core regions of language because we know most about the laterality of these regions, but future lateralization studies could test the view of Fedorenko and Thompson-Schill (2014), among other views on brain mechanisms, to further chart functional and anatomical asymmetries, starting from variations in language lateralization.

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CHAPTER 35

NEURAL MECHANISMS OF MUSIC AND LANGUAGE

MATTSON OGG AND L. ROBERT SLEVC

Introduction

Music and language share the distinction of being among the most uniquely human propensities: both are universally present in cultures throughout the world (Berwick, Friederici, Chomsky, & Bolhuis, 2013; Brown & Jordania, 2011; Hauser, Chomsky & Fitch, 2002; Savage, Brown, Sakai, & Currie, 2015), and are acquired over stereotyped trajectories in development (Hannon & Trainor, 2007; Kuhl, 2004; Trehub, 2003). These parallels, as well as their similar functions as channels of acoustic communication, naturally lead to the supposition that music and language share deeper neural-processing substrates (Brandt, Gebrian, & Slevc, 2012; Heffner & Slevc, 2015; Koelsch, 2005; Patel, 2003; 2008; Schulze & Koelsch, 2012; Slevc & Okada, 2015). At the very least, they tread similar ground as they ascend the auditory pathway.

These similarities aside, why should the study of neurolinguistics be concerned with the processing of music? First, music and language rely on many of the same acoustic computations. In other words, when processing signals in either domain, the brain must solve similar problems. This includes the perception of pitch, spectrotemporal modulation cues, temporal regularities, sound source identification, and "streaming" or tracking an acoustic target through an auditory scene (Bregman, 1990; McAdams & Bregman, 1979; see Poeppel, Cogan, Davidesco, & Flinker, Chapter 26 in this volume). Some of these phenomena are integral and highly developed in music processing. A better understanding of how the brain solves these problems for music can in turn illuminate how they are carried out for language.

This leads directly to the second way in which neurolinguistics can benefit from the study of music: musical traditions rely on conceptual and hierarchical cognitive representations similar to language. These representations have been especially well characterized in Western music (Krumhansl & Kessler, 1982) and, if studied alongside speech and language, perhaps provide a tractable and testable model of how high-level representations are maintained and interfaced with during communication. These representations even lend themselves to hierarchical syntactic (Lerdahl & Jackendoff, 1983; Longuet-Higgins, 1976; Rohrmeier, 2011) and prosodic (Heffner & Slevc, 2015; Lerdahl & Jackendoff, 1983) linguistic analyses.

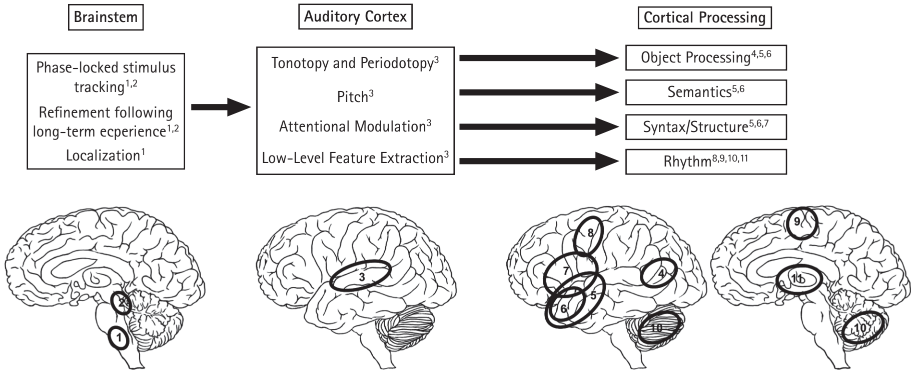
A third manner in which neurolinguistics could profit from an improved understanding of music processing is that music can help us explore and better understand how the listener builds meaning in auditory sequences over time. Exploring the temporal dynamics of how information is coherently integrated as it unfolds requires an understanding of the higher and lower limits of the various cognitive and perceptual processes involved. Music can be a powerful tool in exploring these processes. Examples of this have already been demonstrated in a set of studies examining neural oscillators and their close relation to hierarchical structure building (Doelling & Poeppel, 2015; Ding, Melloni, Zhang, Tian, & Poeppel 2015) and in auditory stream segregation (Bregman, 1990; Bregman & Campbell, 1971; McAdams & Bregman, 1979).

Examining music and language together can also shed light on more general domains of cognition and perception. For example, human listeners have a remarkable ability to focus on a single target sound, such as a voice or instrumental line, despite interference from other voices in a crowded room or symphony. Better understanding this "cocktail party problem" (Cherry, 1953) or auditory "streaming" (Bregman, 1990; McAdams & Bregman, 1979) can further our understanding of attention, object representations, and feature binding beyond audition. Similarly, understanding musical patterns and traditions in terms of their statistical availability in speech signals (Ross, Choi, & Purves, 2007; Schwartz, Howe, & Purves, 2003) can be used to more broadly understand probabilistic models of neuronal connections and their relation to higher-level perceptual tendencies. An excellent example of this comes from research on understanding musical consonance (Bowling & Purves, 2015). Furthermore, examining the mechanisms by which learners develop an understanding for statistical patterns in temporal domains such as music (Loui, Wu, Wessel, & Knight, 2009) and speech (Saffran, Newport, & Aslin, 1996; Saffran, Newport, Aslin, Tunick, & Barrueco, 1997) can inform our understanding of statistical learning more broadly (Zhao, Ngo, McKendrick, & Turk-Browne, 2011).

Finally, the combined study of music and language can inform our understanding of the evolution of interpersonal communication. The topic of the evolutionary interplay between music and language has a long, rich history dating back (at least) to Darwin (1871). A discussion of these issues would warrant its own chapter (Cross, 2007) or book (Mithen, 2005), and will not be addressed in detail here, except to point out how useful the framing of a comparative perspective has proven to be to our understanding of the neural processing of acoustic communicative sounds (Hauser et al., 2002; McDermott & Hauser, 2005). Accordingly, findings from animal work will be described where appropriate to illuminate common neural mechanisms involved in music and language processing that might otherwise be difficult to assess in humans.

The structure of this chapter will follow the neural processing of music and speech as acoustic signals ascending the auditory pathway. Figure 35.1 outlines this processing stream and provides a visual indication of what neural structures are involved. We will describe findings regarding how music and speech are relayed, coded, or processed starting first in the brainstem, then in early auditory processing areas in cortex, followed finally by higher-level cortical regions involved in more abstract cognitive operations. At each step in the processing pathway, we will describe how the auditory system carries out operations common to both types of signals, as well as how the different demands imposed by music or speech are managed by the brain. In doing so, it will often be useful to describe music and speech in terms of both their common and unique acoustic features or characteristics, a perspective that may be helpful for research in this area generally (Giordano, Pernet, Charest, Belizaire, Zatorre, & Belin, 2013; Giordano, McAdams, Zatorre, Kriegeskorte, & Belin, 2012; Samson, Zeffiro, Toussaint & Belin, 2011).

Attention to the unique, acoustic-level processing demands of music and speech will also illuminate how experience in one domain (e.g., musical training, multilingualism) can influence neural processes involved in the other. Plasticity in the auditory pathway resulting from long-term, top-down demands will be described in view of the *OPERA hypothesis* (which stands for Overlap, Precision, Emotion, Repetition, and Attention, Patel, 2011, 2012, 2014), which speculates that increased precision, attention, repetition, and motivation from one domain can influence overlapping neural processes that subserve both domains. Highlighting instances of cross-domain plasticity provides strong evidence that the neural structures involved (and pressed upon by a particular domain, like musical training, for example) are common to processing in both domains.


Brainstem
Phase-locked stimulus tracking1,2
Refinement following long-term ecperience1,2
Localization1
Auditory Cortex
Tonotopy and Periodotopy3
Pitch3
Attentional Modulation3
Low-Level Feature Extraction3
Cortical Processing
Object Processing4,5,6
Semantics5,6
Syntax/Structure5,6,7
Rhythm8,9,10,11
1
2
3
8
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4
5
6
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11
10

FIGURE 35.1. An overview of the processes involved in the perception of music and language and the neural structures that support these functions. Numbers approximately correspond to the auditory and cortical processing hierarchy: (1) olivary complex, (2) inferior colliculus, (3) auditory cortex: Heschl's gyrus/superior temproal cortex, (4) planum temporale, (5) anterior superior temporal cortex, (6) temporal pole, (7) Broca's area (left hemisphere), (8) pre-motor cortex, (9) supplementary motor area, (10) cerebellum, and (11) basal ganglia.

BRAINSTEM

Speech and music enter the ear as acoustic signals and create vibrations in the eardrum, which are transmitted over the ossicles to the oval window and create disturbances in the fluid that fills the cochlea. These disturbances are transduced into electrical signals by hair cells in the basilar membrane and are then transmitted to the brain via the auditory nerves. Incoming signals then pass through nuclei in the brainstem on their way to auditory cortex (see Figure 35.1). Activity within these brainstem nuclei exhibits exceptional temporal resolution. This allows for the critical sound localization computations of inter-aural time and level differences to be performed (Carr & Konishi, 1988). These occur within the medial superior olive and lateral superior olive, respectively (Grothe, 2003). Localization cues rely on sub-millisecond differences in timing (Grothe, 2003; Schnupp & Carr, 2009), and are crucial for auditory streaming (Cherry, 1953).

The robust temporal resolution of the brainstem is realized by temporally phase-locked patterns of neural firing that match the acoustic patterns of incoming stimuli (Smith, Marsh, & Brown, 1975). This phase-locked activity, after a brief transient period following sound onset, can track acoustic patterns up to 1,000 Hz, which covers a variety of key auditory features such as pitch, harmonic information, and some formants. Such cues are crucial to the perception of speech and music, making the brainstem and subcortical responses an especially interesting area of study. Neural activity in the brainstem (specifically, the auditory brainstem response) can be recorded externally by electrodes placed on the scalp (see Leckey & Federmeier, Chapter 3 in this volume), and provides a powerful clinical and research tool (Chandrasekaran, Hornickel, Skoe, Nicol, & Kraus, 2009; Chandrasekaran & Kraus, 2010; Kraus & Chandrasekaran, 2010). The exact neural source of the response recorded at the scalp is not entirely clear, but findings based on timing and temperature ablation indicate that the inferior colliculus (Smith et al., 1975) or superior olive (Hoormann, Falkenstein, Hohnsbein, & Blanke, 1992) may be the principal generators of this signal. However, cortical generation sites have also been suggested by findings in magnetoencephalography (MEG) (Coffey, Herholz, Chepesiuk, Baillet, & Zatorre, 2016; see Salmelin, Kujala, & Liljeström, Chapter 6 in this volume). Nonetheless, electrical correlates of brainstem activity recorded at the scalp provide an amazingly detailed representation of what is being heard—so much so that the amplified playback of (averaged) electroencephalograph (EEG) recordings of responses to speech are intelligible to new listeners (Galbraith, Arbagey, Branski, Comerci, & Rector, 1995).

In recent years, it has become apparent that these brainstem responses are plastic and sensitive to both musical and linguistic long-term experience. For example, the brainstem recordings of speakers of tone languages where pitch differences in speech are an important phonemic cue (in this case, Mandarin) show more robust encoding of pitch information as well as the second harmonic when listening to tonal syllables than speakers of non-tone languages (Krishnan, Xu, Gandour, & Cariani, 2005). Musicians who speak non-tone languages show similarly enhanced brainstem encoding of pitch (Musacchia, Sams, Skoe, & Kraus, 2007) not only when listening to musical tones, but also to syllables from tone languages (Wong, Skoe, Russo, Dees, & Kraus, 2007). The enhanced brainstem responses of musicians are especially strong when listening to the timbre of their primary instrument (Strait, Chan, Ashley, & Kraus, 2012) and to emotive vocal expressions (Strait, Kraus, Skoe, & Ashley, 2009). In general, tone-language speakers and musicians appear to have similar advantages in brainstem response fidelity, compared to non-musician, non-tone-language speakers (Bidelman, Gandour, & Krishnan, 2010). However, there is evidence for some domain-dependent differences between tone-language and musician groups. For example, musicians show enhanced brainstem pitch tracking compared to tone-language speakers when tones in the stimuli correspond to Western musical pitches (see also Bidelman, Gandour, & Krishnan, 2011).

This enhanced brainstem response fidelity is related to behavioral and perceptual benefits as well. Analyses of the spectral properties of musicians' brainstem responses to triads (Bidelman & Krishnan, 2011) and musical intervals (Bidelman & Krishnan, 2009) reveals stronger pitch information than dissonant intervals, which correlates very highly with behavioral judgments of consonance and dissonance. In other words, judgments of consonance follow the standard hierarchy of Western musical theory, with small interval pitch relations being judged as more consonant. These consonant stimuli are also represented more robustly than dissonant ones in brainstem responses. Better speech in noise perception has also been linked to more accurate timing of brainstem responses, with poorer speech in noise perception being linked to longer delays in neural responses, particularly around formant transitions (Anderson, Skoe, Chandrasekaran, & Kraus, 2010). Similarly, more consistently isochronous tapping is associated with better phase locking in auditory brainstem responses (Tierney & Kraus, 2013), and, among preschoolers, is also associated with better early language abilities (Woodruff Carr, White-Schwoch, Tierney, Strait, & Kraus, 2014). Given that musical training can increase the fidelity of brainstem responses, it should be no surprise that the brainstem fidelity benefits of musical training correlate with improved speech in noise perception (Parbery-Clark, Skoe, & Kraus, 2009; Parbery-Clark, Tierney, Strait, & Kraus, 2012) and hearing abilities in other challenging settings, such as in highly reverberant conditions (Bidelman & Krishnan, 2010).

Perhaps less obviously, brainstem response fidelity and speech in noise abilities are also associated with reading ability in children, although potentially in different ways. For example, one study found that models of different brainstem response measures accounted for a large amount of the variability in either reading or speech in noise performance among school-age children. However, the models of brainstem response measures that predicted performance on one outcome measure (reading or speech) did not generalize well when fit to the other outcome measure. This suggests that non-overlapping components of brainstem responses might be associated with reading and speech in noise performance, respectively (Hornickel, Chandrasekaran, Zecker, & Kraus, 2011). Hornickel and colleagues (Hornickel, Anderson, Skoe, Yi, & Kraus, 2012) also suggest that the increased accuracy of brainstem responses and hearing ability aid in children's mapping of acoustic input to orthographic features when learning to read. Encouragingly, when we move beyond correlational findings, musical training has also been shown to improve brainstem response fidelity and speech in noise perception in a randomized trial among school-age children (Kraus, Slater, Thompson, Hornickel, Strait, Nicol, & White-Schwoch 2014) and among adolescents who self-selected musical training compared with a control group who also received extra-curricular training that was not musical (Tierney, Krizman, & Kraus, 2015).

On the other end of the age spectrum, the neural coding of acoustic signals at the brainstem declines as listeners grow older (Anderson, Parbery-Clark, White-Schwoch, & Kraus 2012), and this decline is associated with poorer perception of speech in noise (Anderson, White-Schwoch, Parbery-Clark, & Kraus, 2013). However, musical training can offset these declines in neural acuity and predicts performance on certain perceptual tasks such as categorical vowel perception (Bidelman & Alain, 2015). Taken together, these findings indicate that brainstem responses are very sensitive to both musical and linguistic experience, and align with explanations offered by the OPERA hypothesis (Patel, 2011, 2012, 2014) in that experience in either domain might affect common circuits through repetition of tasks requiring higher auditory acuity. Enhanced brainstem responses to acoustic signals also may be associated with many positive learning and quality-of-life outcomes. Thus, musical training may be a useful tool for accessing these advantages. These benefits are thought to result from top-down cortical modulation that interacts with activity in inferior colliculus via corticofugal pathways while performing these tasks (Chandrasekaran & Kraus, 2010; Tzounopoulos & Kraus, 2009). Notably, these cross-domain benefits would not be possible if music and speech did not share overlapping neural circuitry and were amenable to plasticity (Patel, 2011, 2012, 2014).

EARLY CORTICAL PROCESSING: AUDITORY CORTEX

Early auditory cortical areas receive input from the brainstem (see Figure 35.1) and continue to maintain a detailed representation of the input stimulus (Mesgarani & Chang, 2012; Pasley et al., 2012), however, subsequent processing follows a hierarchical structure, with downstream functions exhibiting more complexity and selectivity (DeWitt & Rauschecker, 2012; Okada et al., 2010; Peelle, Johnsrude, & Davis, 2010). Overall, this approximates a dual-stream, ventral and dorsal, "what" and "where"/"how" organization (Rauschecker & Scott, 2009; Rauschecker & Tian, 2000), similar to vision (Mishkin, Ungerleider, & Macko, 1983). Even though music and language are expressive systems unique to humans, they both rely on basic processes carried out in auditory cortex. These processes are fundamental to extracting features from sounds and thus contribute to later, more complex cognitive functions. Additionally, many auditory cortical functions, particularly in more primary areas, are preserved among mammals (Theunissen & Elie, 2014; Tsunada & Cohen, 2014). Thus, the crucial insights gained from the measurement of neuronal populations in various species, including primates (Hackett, Preuss, & Kaas, 2001; Kaas & Hackett, 2000), ferrets (Chi, Ru, & Shamma, 2005), and guinea pigs (Occelli, Suied, Pressnitzer, Edeline, & Gourevitch, 2015), provide a unique window into the computations being performed at the neural level that subserve the more intricate operations that humans complete when listening to speech and music.

Mapping Primary and Nonprimary Auditory Cortex: Tonotopy and Periodotopy

The first cortical destination for speech, music, and all acoustic signals in humans is primary auditory cortex, which is generally thought to be located in Heschl's gyrus, on the superior plane of the temporal cortex, tucked behind where the temporal and parietal cortices meet (Zatorre, Belin, & Penhune, 2002). Tonotopic organization places neurons that respond to similar frequencies close to each other in cortical geography and thus represents the harmonic and formant structure of speech and musical sounds in a straightforward manner. This maximizes spatial organization and increases the efficiency of downstream processing. The sensitivity of the different frequency responses along this tonotopic axis is especially influenced by the acoustic characteristics of speech (Moerel, De Martino, & Formisano, 2012). Primary auditory cortex is generally defined by its tonotopic organization in response to simple tones and reversals of this tonotopic gradient (low, high, low, etc.). However, considerable debate exists regarding the exact location and boundaries of primary and nonprimary auditory areas in humans (Da Costa et al., 2011). Da Costa and colleagues (2011) used high-resolution functional magnetic resonance imaging (fMRI) (see Heim & Specht, Chapter 4 in this volume) to record functional activity while participants heard a series of low to high tones. The resulting patterns of activation outlined high-to-low-to-high mirror symmetric tonotopic gradients that ran perpendicular to Heschl's gyrus in every participant, with the low portion of the response being at the apex of the gyrus and the higher frequency sensitive areas receding into the sulci on each side. Similar work in fMRI has also implicated Heschl's gyrus, although some specifics, such as the direction of the tonotopic gradients, vary between studies (Formisano et al., 2003; Humphries, Liebenthal, & Binder, 2010). While the certainty of tonotopic organization becomes less clear at the neural level (Bandyopadhyay, Shamma, & Kanold, 2010; Kanold, Nelken, & Polley, 2014), it has nonetheless been a widely used heuristic for mapping human auditory cortex (Da Costa et al., 2011; Formisano et al., 2003; Humphries et al., 2010), localizing basic auditory functions in human fMRI studies (Lewis et al., 2009; Norman-Haignere, Kanwisher, & McDermott, 2013, 2015; Talkington, Rapuano, Hitt, Frum, & Lewis, 2012; Wessinger et al., 2001), and identifying different auditory fields in primates (Romanski et al., 1999; Rauschecker, Tian, & Hauser, 1995).

Additional gradient patterns as well as other weaker tonotopic areas that have been observed near Heschl's gyrus (Formisano et al., 2003; Humphries et al., 2010; Moerel et al., 2012; Wessinger et al., 2001) are very similar to secondary auditory areas measured in primates (Hackett, Preuss, & Kaas, 2001; Kaas & Hackett, 2000) and have been identified as sites whose projections might initiate subsequent processing along the "what" and "where" pathways (Formisano et al., 2003; Kass & Hackett, 1999; Moerel et al., 2012; Romanski et al., 1999; Wessinger et al., 2001). Neighboring "belt" areas in primates respond to tones, but are more responsive to complex stimuli and attributes such as band-passed noise (Romanski et al., 1999) as well as conspecific vocalizations anteriorly (Rauschecker et al., 1995) and location more posteriorly (Tian et al., 1997; Rauschecker & Scott, 2009). An investigation of this dual-stream "what" and "where" processing structure in humans used MRI-guided transcranial magnetic stimulation (TMS; see Schuhmann, Chapter 5 in this volume) to selectively inhibit anterior or posterior auditory cortex (Ahveninen et al., 2013). A double dissociation was found whereby TMS pulses disrupting posterior auditory cortex impaired sound localization performance, while anterior TMS disruption impaired identification, suggesting that this dual-stream specialization is maintained in humans.

Other aspects of sound also appear to be represented by a highly structured organization throughout primary and secondary auditory cortex. These include a mapping of temporal modulation rates (or periodotopy) perpendicular to frequency modulation gradients (Barton, Venezia, Saberi, Hickok, & Brewer 2012). Although the organization of auditory cortex and these temporal modulation gradients may be driven by the organization of tonotopic frequency gradients (Leaver & Rauschecker, 2016), the overlapping organization of frequency and temporal modulation bands together support findings that delineate auditory cortical function in terms of *joint* spectrotemporal dynamics (Hullett, Hamilton, Mesgarani, Schreiner, & Chang, 2016; Santoro et al., 2014; Santoro et al., 2017; Schönwiesner & Zatorre, 2009). This, in turn, might support more complex operations relevant to the perception of speech (Elliot & Theunissen, 2009; Holdgraf et al., 2016) and music (Elliot, Hamilton, & Theunissen, 2013; Theunissen & Elie, 2014).

Adaptive Neural Function: Attending to Goals and Targets

In addition to responding to tonotopic, periodotopic, and spectrotemporal information, early auditory areas modulate their activity based on attentive processing and behavioral goals (Fritz, Elhilali, David, & Shamma, 2007). These attentive modulations support the listener's ability to focus on speech or music in busy auditory scenes, such as in conversations at a cocktail party. Fritz and colleagues found that stimulus-dependent responses to rewarding targets in an operant task modulated receptive fields of neurons in primary auditory cortex toward the features of the rewarding stimuli, and suppressed activity for nearby, non-target acoustic bands (Fritz, Elhilali, & Shamma, 2005; Fritz, Shamma, Elhilali, & Klein, 2003). This pattern of enhancement and suppression of responsiveness in these early areas as a function of task-related goals is thought to sharpen attentiveness to desired stimulus features. In a later study that measured neurons in both primary auditory cortex and frontal cortex, modulations in auditory cortex were found to be driven by top-down activity from frontal neurons, which rapidly gated their responses depending on the demands of the task (Fritz, David, Radtke-Schuller, Yin, & Shamma, 2010). For example, these frontal neurons showed no preference for a tone stimulus in passive listening before the task, but during task performance these neurons modified their activity in response to the same tone when it was now a target and relevant to behavioral goals.

Moving up the processing hierarchy from the simpler receptive fields of primary auditory cortex, attention-modulated stimulus tracking is also observed in nonprimary auditory areas. Tracking a target speaker in the presence of competitor speech is a difficult problem since the signals are intertwined when they reach the ear. Nonetheless, human listeners are able to attend to a given speaker quite easily (Cherry, 1953). A typical paradigm for investigating this phenomenon involves presenting a participant with two streams of speech, and asking him or her to attend or respond to one target, while ignoring the other. Analogous operations are thought to occur when a listener tracks a musical part in a multi-instrumental composition or auditory scene (Bizley & Cohen, 2013; Bregman 1990). Neural correlates of an attended speaker, even in the presence of the competitor, can be reconstructed from neuronal signals in nonprimary auditory areas. Ding and Simon (2012) demonstrated that the temporal envelope of the speech of an attended speaker can be reconstructed from an MEG signal when two overlapping speech signals are delivered to the listener. This representation also demonstrated invariance, as it was not affected by intensity changes to the competitor, a critical feature of auditory objects (Griffiths & Warren, 2004). Furthermore, the fidelity of this representation was found to be a significant predictor of perceptual performance (Ding & Simon, 2013).

Similar attentionally mediated reconstructions have also been generated from electrocorticography (ECoG) recordings in humans undergoing treatment for epilepsy, using neural activity within the high-gamma range (75–150 Hz). One study found that the neuronal reconstructions maintained features of an attended, but not an unattended, speaker, and that these reconstructions were related to performance on a comprehension task (Mesgarani & Chang, 2012). Later work showed that attentional modulation of neural responses is present in earlier auditory areas, showing increased responses to targets relative to distractor speakers, while later stages of processing (mostly beyond auditory cortex) contained only information for the attended speaker, with no trace of the distractor speaker (Zion Golumbic et al., 2013). These reconstruction techniques provide a powerful demonstration of how attention can modulate sensory input, and can adjust the neural representations of complex stimuli in difficult situations at various levels of processing.

Related ECoG findings during music listening suggest that similar mechanisms may be at play. Potes, Gunduz, Brunner, and Schalk (2012) demonstrated that high-gamma activity in posterior STG electrodes tracked the amplitude envelope of musical stimuli, and that other acoustic and timbral features were characterized by electrodes in temporal cortex in a manner similar to speech (Strum, Blankertz, Potes, Schalk, & Curio, 2014). However, these results are based on a single musical work, and the designs did not include attentional modulations or stimulus reconstruction. Thus, it remains to be seen how these patterns of activity during music listening might be modulated by additional cognitive demands. Lyrical portions of the musical work did create the largest response during music listening, suggesting that the lead melody might have primacy in these cortical patterns (Strum et al., 2014). However, without an additional melodic control, this pattern could also be due to a possible primacy of speech processing in the left hemisphere or increased signal density from the addition of vocal parts. It will be exciting to see how this line of investigation develops, and taken with the attentionally modulated findings in speech processing, these timbral and acoustically driven findings during multi-part musical compositions may present an ideal arena for further examining the effects of attention modulated cortical activity in MEG, EEG, or ECoG.

Pitch

In addition to object tracking and streaming, music and speech both rely heavily on the perception of pitch. In music, pitch is central to establishing tonal contexts and composing melodic and harmonic relations. In speech, pitch is vital for intonation and prosodic cues, and is critical for differentiating phonemes in tonal languages. Pitch and spectrotemporal coherence are also fundamental cues used in stream segregation, which is important in both speech and music (Pressnitzer, Suied, & Shamma, 2011; Shamma, Elhilali, & Micheyl, 2011). However, the perception of pitch does not align precisely with fundamental frequency (or a tone's lowest harmonic), and this can complicate investigations of pitch processing: Does a neural response reflect tonotopic activation, or the perception of pitch (Norman-Haignere et al., 2013)? Thus, the investigation of the neural substrates of pitch requires creative experimental designs and stimuli.

One powerful tool has been the use of the *missing fundamental* phenomenon, wherein the fundamental frequency of a harmonically complex tone can be removed completely, while leaving the rest of the tone's harmonic structure intact. Despite the loss of the fundamental frequency, the perception of the tone's pitch is not impaired due to the regularity of the tone's harmonics, which correspond to integer multiples of the tone's fundamental (Von Békésy, 1972). This is quite a common phenomenon in telephone communication (as the telephone network is band-limited, only transmitting frequencies between ~300 Hz and 3,400 Hz) or when listening to music through small speakers. The output of such devices does not extend to the lowest frequencies of some voices or instruments where the fundamental resides. The ability to perceive pitch despite the absence of the fundamental has also been observed in cats (Heffner & Whitfield, 1976), primates (Tomlinson, & Schwarz, 1988), and infants (Clark & Clifton, 1985). Using this to their advantage, Bendor and Wang (2005) recorded neuronal responses from primates while they played tones with and without a fundamental frequency. A set of neurons on the anterior edge of primary auditory cortex responded to both stimuli, meaning they were responsive to pitch over and above tonotopic responsiveness.

The findings in primates align closely with fMRI evidence in humans. Studies that manipulate pitch chroma (the notes of a piano within an octave) independently of pitch height (the location of the octave on a piano; Warren, Uppenkamp, Patterson, & Griffiths, 2003) find pitch-responsive activation in anterolateral Heschl's gyrus. A similar pattern of activity is found in studies that are able to manipulate pitch salience via resolved and unresolved harmonics (Norman-Haignere et al., 2013; Penagos, Melcher, & Oxenham, 2004), and studies that employ varying levels of harmonic structure in pitches created by regular-interval noise complexes (Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002). Similar regular-interval noise stimuli have been used in a study of direct neural recordings in human epilepsy patients. This study found that neuronal populations tracked stimulus regularity in the noise throughout Heschl's gyrus, but high-gamma oscillatory activity, a hallmark of neural activity related to attention, only emerged when the regularity of the stimuli was within the range that pitches can be perceived in humans (above approximately 30 Hz; Griffiths et al., 2010). However, this study found high-gamma activity to be maximal in an area of Heschl's gyrus more medial to the lateral areas identified in fMRI, indicating that more research is needed to bridge these bodies of work.

A special case in human pitch perception exists that may shed additional light on these neural processes and differences in the processing requirements of speech and music. Deutsch, Henthorn, and Lapidis (2011) reported a phenomenon wherein regularly spoken sentences appeared to transform into more melodic sequences, similar to music, with repeated listening. This has been called the *speech to song illusion* (Deutsch et al., 2011). While the acoustic and psychological mechanisms that allow a speech utterance to transform into a melodic utterance are still under debate (Falk, Rathcke, & Dalla Bella, 2014; Vanden Bosch der Nederlanden, Hannon, & Snyder, 2015a), this illusion provides a fascinating opportunity to examine parallels between music and speech processing (Vanden Bosch der Nederlanden, Hannon, & Snyder, 2015b). One fMRI study (Tierney, Dick, Deutsch, & Sereno, 2012) measured functional changes in participants while listening to stimuli that did and did not induce this illusion (transforming from speech to song) and found that when the sentence had "converted" from speech to music, various neural areas involved in music and melodic processing were activated relative to when it was perceived as speech. Notably, this included the same lateral area of Heschl's gyrus described in previous fMRI studies that responded specifically during the perception of pitch. That this area was activated more when the perception of pitch and melodic information was emphasized, despite the consistency of the incoming acoustic information, is powerful evidence that activation in this area is linked to the psychological experience of pitch, rather than other acoustic stimulus features.

The Influence of Experience on the Structure of Early Auditory Processing Areas

Could producing or paying attention to different kinds of stimuli, like speech or music, over long periods of time be associated with particular structural changes in auditory cortices? Such a result would align with the view of the OPERA hypothesis (Patel, 2011, 2012, 2014), and a variety of findings suggest that there are associations between brain structure and listening abilities. Golestani and colleagues (2007) found that participants who learned the speech sounds of a new language the fastest also had greater white-matter density in left Heschl's gyrus and were five times more likely to have an anatomical split or duplication of this area. This pattern was echoed by Wong and colleagues (2007), who found a similar relationship between left Heschl's gyrus volume (but in gray rather than white matter) and learning linguistic cues that incorporated pitch. This was further explored in a later study that examined expert phoneticians (Golestani, Price, & Scott, 2011): expert phoneticians, compared with controls, had larger transverse gyri and were more likely to have split gyri. However, these patterns in auditory cortices were not associated with years of transcription training, leading the authors to hypothesize that these neuroanatomical differences created an aptitude for phonetic processing in these individuals that preceded their phonetic training.

Anatomical differences in Heschl's gyrus have also been found in musicians relative to non-musicians (Gaser & Schlaug, 2003). However, Bermudez and Zatorre (2005) found anatomical differences in musicians relative to controls in areas posterior and anterior to Heschl's gyrus. Nevertheless, structural differences in Heschl's gyrus translate into superior music perception abilities and stronger neural responses to tones early in processing (Schneider et al., 2002). These findings were replicated in a later study, which also observed that morphological differences associated with musical experience were not associated with an inclination to resolve pitch differences based on fundamental frequency or spectral cues to pitch (Schneider et al., 2005). While not related to musical training (but see Seither-Preisler et al., 2007), a participant's inclination to resolve pitch based on fundamental frequency or spectral cues was found to be associated with greater volumes of left and right Heschl's gyrus, respectively (Schneider et al., 2005). Warrier and colleagues (2009) went a step further by examining how individual variation in the structure of Heschl's gyrus related to individual differences in the *functional* processing of temporal or spectral complexity. They found that individual differences in Heschl's gyrus *anatomy* were highly correlated with individual differences in the geographical extent of *functional* neural responses to temporal (left hemisphere) or spectral (right hemisphere) processing.

Structural and functional changes related to musical training or language experience can also be observed beyond primary areas. Moreover, plastic changes following musical training or exposure may also be induced very early in development. Zhao and Kuhl (2016) found that 9-month-old infants exposed to triple-meter rhythmic patterns (via random assignment) had greater functional response sensitivity in frontal and auditory areas to rhythmic deviations in both speech and music compared to controls. Motor areas, in particular, seem to be related to proclivities in music and language production. Perhaps the most salient example is the relationship between handedness and language dominance of the contralateral hemisphere (see Van der Haegen & Cai, Chapter 34 in this volume). Knecht and colleagues (2000) demonstrated a parametric relationship between the strength of an individual's handedness and dominance of the contralateral hemisphere in a word-production task among left-handed and ambidextrous participants. Musical training also appears to increase the size of functional responses in motor cortex specific to a musician's main instrument (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995) and also results in stronger responses in tonotopic areas to harmonically rich tones compared to controls (Pantev, Oostenveld, Engelien, Ross, Roberts, & Hoke, 1998). Structural changes are also found in motor areas and the corpus callosum following as little as 15 months of training (Gaser & Schlaug, 2003; Hyde et al., 2009). These changes, particularly white-matter changes in corpus callosum, may also be subject to a critical period prior to 7 years of age (Steele, Bailey, Zatorre, & Penhune, 2013).

It should be noted that in all of the previously described findings it is difficult to disentangle effects of experience, such as musical training or linguistic exposure, from those of predispositions to a certain vocation or activity that are enabled by abilities derived from neural anatomy. Both likely play a role; for example, Golestani and colleagues (2011) hypothesized that left Heschl's anatomy preceded and influenced phoneticians' abilities, rather than stemming from experiential effects. On the other hand, Golestani and colleagues (2011) also found that the surface area of the left *pars opercularis* (the anterior part of Broca's area) in phoneticians was related to their amount of phonetic transcription training, fitting with other work suggesting that anatomical differences reflect experience-dependent plasticity (e.g., Herholz & Zatorre, 2012; Münte, Altenmüller, & Jäncke, 2002). This could be due in part to evidence for positive changes in auditory cortices and abilities following even a relatively short (15-week) training regimen (Hyde et al., 2009). It may be that "nature" and "nurture" are both at play in speech and language development, as well as anatomical plasticity, but that experience affects plasticity differently for music and language processing. In any case, changes observed within Heschl's gyrus and other parts of auditory cortex tend to be associated with benefits to lower-level discriminative abilities and do not necessarily translate into the higher-level cognitive benefits that musical experience may (e.g., Slevc, Davey, Buschkuehl, & Jaeggi, 2016) or may not (e.g., Bigand & Poulin-Charronnat, 2006; Schellenberg, 2015) engender.

Acoustic Feature Extraction: Instruments, Speakers, and Phonemes

Many of the in-depth fMRI studies that seek to identify the neural processing substrates of music and language in humans find overlapping activation in early auditory cortices.

These activation patterns are typically thought to be involved in low-level acoustic feature extraction, and the focus in these studies turns instead to higher cortical areas specialized for processing one domain specifically (Leaver & Rauschecker, 2010; Norman-Haignere et al., 2015). However, we know from animal work and some fMRI work that a wide variety of interesting acoustic computations are going on at these early stages, which might serve to sort or direct incoming signals for later analyses by more specialized higher-level areas (Bizley & Cohen, 2013; Theunissen & Elie, 2014; Tsunada & Cohen, 2014). Indeed, these acoustic components are bound to early perceptual units such as phonemes or notes. We have already touched on some of these components, such as location information, pitch, and how the perception and processing of these features may be modulated by attention. But, at this early stage, the brain is also trying to decode the source or identity of a given sound, and similarly, to sort incoming information into more manageable subcomponents like auditory objects.

Sound sources in music are referred to as *timbres*. Timbre encompasses the acoustic properties or features that distinguish the sounds of different instruments from one another while pitch and loudness are kept equal. Timbre typically refers to a combination of spectrotemporal attributes or dimensions that distinguish a set of instruments (Elliot, Hamilton, & Theunissen, 2013; McAdams & Giordano, 2010; McAdams, Winsberg, Donnadieu, De Soete, & Krimphoff, 1995). Timbre analogs in the speech domain are twofold. First, when viewed in terms of unique spectrotemporal cues, timbre is often operationally defined by different vowels (Town, Atilgan, Wood, & Bizley, 2013), whose first and second formant frequencies create characteristic peaks in the spectral pattern of a sound token (Hillenbrand, Getty, Clark, & Wheeler, 1995). Second, timbre in speech could refer to the characteristic, identifiable features of an individual speaker's voice. Understanding how individuals are identified by voice presents an empirical problem that, like musical timbre, is not completely understood but is defined by a multidimensional set of relevant acoustic cues (Creel & Bregman, 2011; Elliot & Theunissen, 2009; Schweinberger et al., 2014). Much of the complex processing required to extract and interpret these acoustic cues begins in auditory cortex. Indeed, this information must already be accessible at early auditory stages to tune attention to certain speaker targets in the studies on attentive processing and streaming mentioned previously (Mesgarani & Chang, 2012; Pasley et al., 2012; Zion Golumbic et al., 2013). Also, timbre and pitch both rely on similar spectral cues and can interact with one another (Krumhansl & Iverson, 1992; Melara & Marks, 1990). Thus, where does timbral perception fit into early auditory decoding?

A good deal of information pertinent to the source of a sound can be decoded from primary auditory cortex, including areas shared with other mammals. Representations of instrumental timbres based on a computational model of ferret primary cortex can provide enough information for a machine-learning algorithm to identify an extremely large set of instruments with over 98% accuracy, and where this algorithm fails, it confuses stimuli in a manner similar to humans (Patil, Pressnitzer, Shamma, & Elhilali, 2012). Similarly, using in vivo recordings from ferret auditory cortex while listening to a speech corpus, Mesgarani and colleagues (2008) found that responses from subpopulations of neurons matched the spectrotemporal features of vowels and consonants. These populations also contained mappings of dimensions related to formant frequencies in vowels or place and manner of articulation in consonants (which, like vowels, are differentiated by unique spectrotemporal features). Again, a pattern classifier trained on the neural data performed similarly to human listeners on identification judgments and made a similar pattern of confusions on the task. The temporal dynamics of this coding regime were recently investigated by comparing human performance on identifying vowels at varied stimulus presentation durations (2 to 128 ms) with neural responses in guinea pigs to the same temporally constrained tokens (Occelli, Suied, Pressnitzer, Edeline, & Gourévitch, 2015). Many vowels could be identified in the neural data based on the unique characteristics of certain vowels and matching spectrotemporal tuning patterns of individual neurons. These neuronal responses could be used to reliably identify vowel stimuli, even at the extremely short durations. In contrast, human performance was near chance at the shortest durations, although it improved rapidly, plateauing to near ceiling performance around 16 milliseconds. However, while the neural response accuracy did improve some with longer stimuli, it never approached ceiling. This disconnect between behavioral responses and the information carried in neural responses of auditory cortex indicates that behavior is subject to many intervening processing steps, but that much of the necessary information needed for accurate identification can, in principle, be gleaned from primary auditory areas.

A collection of studies by Bizley, Walker, and colleagues (2009, 2011) sought to identify how processes involved in pitch, location, and timbre extraction were collectively organized in primary auditory cortex by presenting ferrets with different combinations of all three cues. Four locations, vowels (timbres), and fundamental frequencies were all crossed, resulting in 64 stimuli. Results of the first study (Bizley et al., 2009) revealed that these processes were highly overlapping, and intermingled in auditory cortex. Neurons often responded to different levels of multiple dimensions. Timbre and pitch, in particular, tended to covary and were somewhat more differentiated from location. A later study (Walker et al., 2011) found that within individual neurons, sensitivity to certain dimensions and information rates tended to cluster into certain anatomical areas. Additionally, many neurons relayed information for multiple acoustic dimensions throughout the time course of their responses. Building on this work, Allen, Burton, Olman, and Oxenham (2017) showed that acoustic variation among the dimensions of pitch and timbre (operationalized as spectral centroid, or brightness) produced largely overlapping patterns of activation in the fMRI responses of humans. However, similar to the findings in ferret auditory cortex (Bizley et al., 2009; Walker et al., 2011), the pitch and timbre changes that they presented to the participants could be decoded from patterns of activity within this area of common activation. Together, these studies emphasize not only how intricately woven together timbre, location, and pitch sensitivity are in auditory cortex, but also that mechanisms are already in place at these early areas to parse and transmit the multidimensional world of sound. As Walker and colleagues point out, these multiplexed response patterns may aid in feature binding for object perception in downstream cortical and cognitive operations.

Before moving on from auditory cortex to later cortical structures that support language and music processing, let us review how the processes just described fit with the OPERA hypothesis (Patel, 2011, 2012, 2014). Functional and structural changes can be observed following musical (and potentially linguistic) training at these early stages of cortical processing (albeit less consistently demonstrated in cortical auditory areas than at the brainstem). In particular, there is evidence for the functional adaptability of auditory cortical receptive fields via top-down attentional biases. This attentional component and its early acoustical processing targets represent two prerequisites that the OPERA hypothesis suggests are required for music to tune processes related to speech: attention and overlap. Given the salience of pitch in speech and music-perception tasks, the neural mechanisms for pitch could also make for an ideal target for attentional modulation. Indeed, in most instances where plasticity has been demonstrated (following long-term experience with tone languages and music), there is a strong bias toward features related to pitch, suggesting that it is a useful target for attentional focus all the way down to subcortical processes, as pointed out by Patel (2012).

Cortex

Human neocortex is responsible for many of the characteristics that set humans apart from the rest of the animal kingdom. Given how unique speech and music are among our species, it is no surprise that these faculties rely heavily on these evolutionarily newer cortical areas. Indeed, language is the tool with which we are able to consider, describe, and wrestle with abstract notions. Hierarchical models of auditory processing and many strong findings suggest that increasingly complex representations and concepts are built up from the acoustic to the more abstract as processing advances from auditory cortices and progresses along the superior portions of the temporal lobes in the ventral pathway (Bizley & Cohen, 2013; DeWitt & Rauschecker, 2012; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; Tsunada & Cohen, 2014). The following sections will outline how music and language rely on both unique and domain-general cortical operations beyond typical auditory areas to successfully execute the operations that result in our everyday experience of music and language (see Figure 35.1).

A number of studies have taken a high-level, comparative approach to examining how music and language may or may not be preferentially processed throughout cortex using fMRI. These studies typically involve presenting participants with stimuli from a wide variety of sound categories, and having the participant respond to noncritical targets to simply maintain attention. Leaver and Rauschecker (2010) presented participants with a variety of 300 millisecond tokens from a variety of sound categories such as musical instruments, speech, and other animal vocalizations. They found overlapping, non-category-specific activity in areas near primary auditory cortex, but found more distal regions that responded preferentially to speech in middle superior temporal gyrus and sulcus, and regions that responded preferentially to music on the more medial surface of right anterior superior temporal cortex, even after statistically controlling for a set of acoustic features of the stimuli. Rogalsky, Rong, Saberi, and Hickok (2011) focused on hierarchical structure processing in language, presenting sentences, scrambled sentences, and novel melodies to participants, and found patterns of activation similar to Leaver and Rauschecker (2010) for melodies (medial and anterior temporal cortex) and for sentences (lateral temporal cortex) when amplitude envelope modulation was controlled for. Angulo-Perkins and colleagues (2014) played longer, 1.5-second-long sentences and melodies, in addition to animal vocalizations and environmental object sounds, and found a strong preference for musical sounds in right anterior superior temporal cortex, while speech demonstrated extensive activation in more lateral areas of superior temporal cortex. Another study by this group (Armony, Aubé, Angulo-Perkins, Peretz, & Concha, 2015) found that the same area of cortex only expressed adaptation to music, not to other auditory stimuli.

Norman-Haignere, Kanwisher, and McDermott (2015) played an extensive and varied set of 2-second musical, vocal, nonvocal, mechanical, and environmental sounds to participants and performed a voxel decomposition analysis to examine the underlying neural response profiles. They found six components that covered different parts of cortex: the first two followed tonotopic gradients, and the second two responded to spectrotemporal modulation patterns in the stimuli. These first four components accounted for all non-speech and non-musical sounds in the stimulus set and were located most proximally to primary auditory areas. The last two components, however, corresponded only to speech (extending laterally from primary auditory areas), and music (extending posteriorly and anteriorly from primary auditory areas), but no strong hemispheric differences were apparent. Taken together, these findings indicate that areas of cortex dedicated to processing speech sounds exist extending along superior temporal sulcus (see also Overath, McDermott, Zarate, & Poeppel, 2015), while areas specific to processing musical sounds exist more anteriorly and medially to these speech areas.

It should be noted, however, that while some studies include factors accounting for acoustic properties as covariates, these studies largely maintain relatively high-level views of music and speech. Indeed, the varied stimulus sets described beg the question of what preferential activation for speech and music at a broad, categorical level really indicates about the underlying neural computations or functions involved. It is similarly difficult to interpret activation from regions that demonstrate overlap between domains. This issue requires a deeper examination of the constituent parts of these signals, both conceptually (phonemes, musical consonance) and acoustically (temporal structure, fine spectral processing). As one example, a study by Giordano and colleagues (2014) found category-specific activations to music, speech, and environmental sounds similar to previous studies in both active and passive listening scenarios, but showed that much of this activation could be explained by a theoretically driven set of acoustic covariates. Other work examining environmental sounds and objects similarly emphasizes the importance of acoustic features in the neural responses to sound (Giordano, McAdams, Zatorre, Kriegeskorte, & Belin, 2013; Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; Lewis et al., 2009; Lewis, Talkington, Tallaksen, & Frum, 2012; Samson et al., 2011).

Categorical Perception and Processing in the Ventral Auditory Pathway

As acoustic processing proceeds from primary auditory areas, computations become more object-oriented and abstract (Lewis et al., 2012; Rauschecker & Scott, 2009). This is beneficial in that it allows us to perceive the identity of a phoneme, for example, consistently in different contexts and across speakers, despite the acoustic changes that may be introduced by acoustic interference or individual speakers. In primates, superior temporal gyrus is responsible for decoding conspecific calls before they are projected to ventral prefrontal cortex (Russ, Ackelson, Baker, & Cohen, 2008; Tsunada & Cohen, 2014), where more abstract features are coded (Cohen, Hauser, & Russ, 2006), integrated with spatial information (Cohen, Russ, Gifford, Kiringoda, & MacLean, 2004), and used in behavioral decisions (Cohen et al., 2009). A similar organization is found for speech along the superior temporal gyrus, particularly in the left hemisphere. In a meta-analysis of neuroimaging findings from studies of language, DeWitt and Rauschecker (2012) observed a progression in sensitivity from phonemic processing in middle superior temporal gyrus, to words in anterior superior temporal gyrus, and finally to phrases in anterior superior temporal sulcus. A similar hierarchical representation can be found for musical stimuli from primary auditory areas to more anterior locations along the superior temporal lobe, perhaps more strongly localized to the right hemisphere (Zatorre et al., 2002). The robust representation of phonemic information in superior temporal gyrus was also demonstrated via direct neural recordings (Mesgarani, Cheung, Johnson, & Chang, 2014). ECoG recordings while participants listened to a corpus of English sentences allowed researchers to capture all of the salient phonemic units of English, which allowed them to then decode the response profiles of neurons and groups of neurons to each phoneme. Subpopulations of neurons could, together, represent the salient acoustic features of individual consonants and vowels and even encoded salient articulatory cues like voice onset time and formant frequencies.

A particularly remarkable aspect of human phoneme perception is its robust categorical nature; that is, sounds that vary along a continuous underlying dimension are perceived as belonging to discrete groups, rather than changing gradually with the changed dimension. This is marked by insensitivity to differences among group members and high sensitivity between exemplars belonging to different groups, despite the same absolute difference in the underlying dimension. It is these perceptual categories that help a listener encode the wide range of phonemes that are essential to language, even when the specific acoustics of a given phoneme vary as a function of noise, distortion, or dynamics of the speaker. This perceptual phenomenon is particularly salient among speech phonemes (Liberman, Harris, Hoffman, & Griffith, 1957), and has even been argued to be unique to speech (Eimas, 1963; Mattingly, Liberman, Syrdal, & Halwes, 1971). However, categories of speech phonemes can be learned by animals that do not possess language, including the chinchilla (Kuhl & Miller, 1975), Japanese quail (Kluender, Diehl, & Killeen, 1987), and budgerigars (Dooling & Brown, 1990). Categorical perception has also been demonstrated for sequential (Siegel & Siegel, 1977a, 1977b; Burns & Ward, 1978; Burns & Campbell, 1994) and simultaneous musical intervals (Zatorre & Halpern, 1979) among musicians, and in some cases for single tones among musicians with absolute pitch (Siegel & Siegel, 1977a; Burns & Campbell, 1994; Miyazaki, 1988). Notably, the findings in animals and among musicians emphasize the importance of experience, since naïve animals and non-musicians do not perceive continuous changes between stimuli in this manner.

fMRI evidence in humans implicates the superior temporal sulcus in the support of these highly categorical percepts. In speech, activation from learned phonemic categories activates regions of left middle superior temporal gyrus more than (non-categorical) complex acoustic stimuli (Libenthal, Binder, Spitzer, Possing, & Medler, 2005). However, other studies that examine specific patterns of voxel activation within the fMRI signal implicate Broca's area (Lee, Turkeltaub, Granger, & Raizada, 2012). This activation is in some cases in addition to activation in left superior temporal gyrus, as well as parietal and motor areas. Left superior temporal gyrus may be most responsive in low noise situations, whereas activation in Broca's and motor areas may be more reliably observed in noisier situations (Du, Buchsbaum, Grady, & Alain, 2014).

Chang and colleagues (2010) provided a particularly strong demonstration of the categorical nature of representations of speech phonemes in superior temporal gyrus at the neural level with ECoG. Using direct recordings of activity in superior temporal gyrus, they found that phonemic categories could be decoded from distributed recording sites. A classifier trained on the neural responses performed best at the peak in neural activity 110 milliseconds after phoneme onset, and confused phonemes in a manner similar to the behavioral performance of the participants. Later results suggest that the neural encoding of phonemes in superior temporal gyrus (along with predictions from frontal cortex) might support the phoneme restoration effect wherein part of a word is perceived even though it has been acoustically masked (Leonard, Baud, Sjerps, & Chang, 2016). Interestingly, fMRI studies of categorical perception for musical intervals implicate similar superior temporal structures in the right hemisphere based on adaptation and discrimination paradigms (Klein & Zatorre, 2011), and through the use of multi-voxel pattern analysis (Klein & Zatorre, 2015). This agrees with processing asymmetries that have been proposed for left and right hemispheres that best suit speech and language operations, respectively (Zatorre et al., 2002).

Sound Sources: Timbres, Speakers, and Questions of Hemispheric Specialization

In addition to phonemic information, speech carries identifiable information pertaining to the identity of the speaker. Indeed, this is especially pertinent to the field of forensic phonetics, which assists in legal or investigative settings where accurate speaker identification might be required (Jessen, 2008; Köster, Hess, Schiller, & Künzel, 1998; Nolan, 1991). A complete accounting of the acoustic landmarks that are important to speaker identity are still somewhat unclear, but speech signals contain cues from features of the vocal folds and vocal tract that can be used to indicate the speaker's size and gender (Creel & Bregman, 2011; Elliot & Theunissen, 2009; Schweinberger et al., 2014). The correspondence between specific physical cues in speech signals and the identity of individuals is similar to that of face perception in the visual modality (Latinus & Belin, 2011; Von Kriegstein, Kleinschmidt, Sterzer, & Giraud, 2005). Faces are known to be processed by specialized areas in cortex (Kanwisher, McDermott, & Chun, 1997), leading some investigators to wonder if the same is true of voices. Belin and colleagues (2000) played participants a wide variety of synthetic and natural stimuli and found a portion of anterior superior temporal cortex that was especially sensitive to the human voice, which they termed the *temporal voice area* (Belin, Fecteau, & Bedard, 2004). This was echoed by another study that employed an fMRI adaptation paradigm while subjects listened to blocks of the same utterance made by 12 different speakers, or blocks of the same speaker making 12 different utterances (Belin & Zatorre, 2003). The difference in activation between these two blocks demonstrated that an area in the right anterior superior temporal cortex was highly active throughout the multi-speaker blocks and was engaged to a greater degree than the multi-syllable blocks, indicating that this area of cortex is sensitive to differences between speaker's voices. Follow-up work has demonstrated that this area can be modulated by attention to the speaker rather than the linguistic content of an utterance (Bonte, Hausfeld, Scharke, Valente, & Formisano 2014; Von Kriegstein, Eger, Kleinschmidt, & Giraud, 2003), or by the recognition of familiar speakers (Von Kriegstein, & Giraud, 2004), and can dynamically interact with the fusiform face area (Von Kriegstein et al., 2005). Multi-voxel pattern analysis techniques have also been used to decode the identity of individual speakers from right anterior superior temporal cortex, as well as from superior temporal cortex bilaterally (Bonte, Hausfeld, Valente, & Formisano 2014; Formisano, Martino, Bonte, & Goebel, 2008).

Other evidence for the importance of these right-hemisphere areas in voice-identity processing comes from cases of phonagnosia. Patients with phonagnosia cannot identify individuals by voice, often as a consequence of a lesion to their right temporal lobe (Hailstone, Crutch, Vestergaard, Patterson, & Warren, 2010; Van Lancker, Cummings, Kreiman, & Dobkin, 1988; Van Lancker, Kreiman, & Cummings, 1989; review: Slevc & Shell, 2015). This cortical specialization may have arisen in our ancestors, as it is present in other mammals that rely on voice identification, such as dogs (Andics, Gácsi, Faragó, Kis, & Miklósi, 2014) and macaques (Perrodin, Kayser, Logothetis, & Petkov, 2011; Petkov et al., 2008).

A parallel line of research also implicates this area in timbre processing. Indeed, many of the processes involved in identifying speakers and timbres are similar: multidimensional representations (McAdams & Giordano, 2009; Theunissen & Elie, 2014), the need to identify a target by matching it to a representation based on its salient acoustic features (Bizley & Cohen, 2013), and using these features to separate targets from the background of an acoustic scene (Pressnitzer et al., 2011). Findings from patients with right anterior hemispheric lesions, which overlap with the voice-processing areas discussed previously, indicate that the resolution of spectral and temporal cues involved in timbral judgments may also rely on right anterior temporal lobe structures (Samson, 2003). In these studies, patients with left and right anterior temporal lobe lesions were asked to discriminate (Samson & Zatorre, 1994) or rate the similarity of synthetic tones that varied in their onset times (temporal manipulation) or number of harmonics (spectral manipulation; Samson, Zatorre, & Ramsay, 2002). Patients with right-hemispheric lesions were particularly impaired at discriminating temporal and spectral cues, and their perceptual spaces based on multidimensional scaling of similarity ratings were distorted relative to left-hemisphere patients and controls (Samson & Zatorre, 1994; Samson, Zatorre, & Ramsay, 2002). Interestingly, some cases of phonagnosia associated with anterior temporal lobe dysfunction are also comorbid with a reduced ability to recognize and discriminate different musical instruments (Hailstone et al., 2010).

Taken together, these results suggest that the ability to identify individual speakers and the ability to perceive differences in instrumental timbres may both rely on the right anterior temporal lobe. It seems that in both cases, the brain is solving a similar problem, potentially by utilizing similar cues to identify the source of a complex sound. Timbre itself is an area of music perception that has not received a good deal of direct focus (but see Allen et al., 2017, Menon et al., 2002; Warren, Jennings, & Griffiths, 2005), but it is implied and inherent in many of the other studies of music and language processing that use a varied set of musical stimuli (Angulo-Perkins et al., 2014; Armony et al., 2015; Leaver & Rauschecker, 2010; Norman-Haignere et al., 2015). Notably, these studies all implicate the right anterior temporal lobe (or planum polare) and necessarily incorporate different timbral stimuli in their manipulations. These findings using more naturalistic stimuli also appear to engage more anterior areas in temporal cortex than studies examining timbre with more controlled (synthesized) stimuli (Allen et al., 2017; Menon et al., 2002; Warren et al., 2005). In a direct comparison of various sound sources that were controlled for pitch and spectral modulation, utilizing multi-voxel pattern analysis methods previously employed for speaker identification, Staeren and colleagues (2009) found large distributed activation patterns that were involved in the decoding of sound sources, whether it was a human or animal vocalization or an instrument. Notably, the areas that aided in the decoding of Staeren and colleagues' sounds extended further along superior temporal gyrus in both hemispheres than the voxels involved in the decoding of the pitch of the tones, which were clustered around more primary areas. Thus, the small body of work comparing speaker and timbre discrimination suggests a set of related neural processes; however, there is a need for further work directly comparing tasks involved in speaker identification and tasks involved in instrumental timbre discrimination.

One explanation for potentially overlapping processes in speaker and timbre identification is that they both rely on large time-scale spectral cues (Warren et al., 2005; Warren, Scott, Price, & Griffiths, 2006). A number of studies (Menon et al., 2002; Warren et al., 2005; Warren et al., 2006) have suggested that an area in the posterior temporal lobes, known as planum temporale, is involved in analyzing these spectral cues (Griffiths & Warren, 2002). Others have also suggested that such analyses are preferentially processed in the right hemisphere (McGettigan, & Scott, 2012; Poeppel, 2003; Zatorre et al., 2002). The sensitivity of the right hemisphere to spectral information has been well established (Schönwiesner, Rübsamen, & Von Cramon, 2005; Zatorre & Belin, 2001). Moreover, right-hemisphere structures are especially responsive to slower temporal modulation rates (Belin et al., 1998; Boemio, Fromm, Braun, & Poeppel, 2005), which allows for the processing of spectral complexity given inherent trade-offs in time and frequency resolution (Zatorre et al., 2002). McGettigan and Scott (2012) also discuss a right-hemisphere advantage for spectral processing, and emphasize that this right-hemisphere sensitivity is more consistent across studies than findings of greater sensitivity to faster temporal modulations in the left hemisphere.

Syntactic and Structural Operations

Syntactic rules allow for long-distance dependencies and hierarchical or referential relations among concepts in sentences. Like speech and language, music is also constrained by a set of rules and hierarchies. Indeed, Western music has an exceptionally well-characterized representational structure that even lends itself to hierarchical analysis using tools developed in linguistics (Granroth-Wilding & Steedman, 2014; Heffner & Slevc, 2016; Katz & Pesetsky, 2011; Krumhansl & Kessler, 1982; Lerdahl & Jackendoff, 1983). The hierarchical structure of music comes from the importance of certain notes within a musical scale and influences the tonal relationships in the natural development of a musical piece. Such a harmonic progression typically begins by establishing a tonal context or structure, then subtly deviating from that context to create tension before finally resolving that tension back at the original tonal center. The context of a musical sequence is established by harmonic relationships between notes or chords early in a sequence, and is actively updated as new harmonic information arrives, as in the case of a key modulation (Krumhansl & Kessler, 1982). A harmonic structure then facilitates expectancies and processing for new information that fits within it (Bigand, Poulin, Tillmann, Madurell, & D'Adamo, 2003). The creation of tension or ambiguity in a harmonic structure is a valuable tool for composers and performers and is thought to be responsible for much of the emotional power of music (Huron, 2006; Krumhansl, 2002; Meyer, 1956). The relations between pitches, keys, and harmonic components can be mapped onto the surface of a toroid, or inner-tube-like shape (Krumhansl &

Kessler, 1982). These relations and to some degree even this representational shape itself are maintained in cortex and are updated as a musical sequence moves through tonal space (Janata et al., 2002). If the proper parallels are drawn, music could be a powerful tool for understanding how abstract representations are engaged and updated in the brain during online tasks, providing an excellent test of many linguistic principles and questions.

A cardinal feature of both music and language is how they unfold over time. A particularly vibrant subject of debate concerns how music and speech may or may not share neural resources to temporally and sequentially integrate acoustic information into coherent wholes (Ding et al., 2015; Doelling & Poeppel, 2015, Patel, 2003; Peretz & Coltheart, 2003; Peretz, Vuvan, Lagrois, & Armony, 2015). Current findings on the topic of shared neural resources for the structural and syntactic processing of speech and music are split. Lesion studies indicate that agrammatism and atonalia can occur independently from one another and stem from double-dissociable patterns of neural damage (Peretz, 1993; Peretz & Coltheart, 2003; Slevc, Faroqi-Shah, Saxena, & Okada, 2016), implying separate neural substrates for structural processing in music and language. Meanwhile, fMRI (Janata, Tillmann, & Bharucha, 2002; Koelsch, Gunter, Zysset, Lohmann, & Friederici, 2002; LaCroix et al., 2015; Oechslin, Van De Ville, Lazeyras, Hauert, & James, 2013; Peretz et al., 2015) and MEG (Maess, Koelsch, Gunter, & Friederici, 2001) studies tend to indicate that processing musical structure activates areas of the brain also implicated in language and working memory, particularly left inferior frontal areas. Additionally, event-related potential (ERP) studies (Minati et al., 2008; Patel, Gibson, Ratner, Besson, & Holcomb, 1998) have shown parallels in electrophysiological signatures associated with musical and linguistic structural irregularities.

This divide has led to the suggestion by Patel (2003) that music and language have independent long-term storage substrates (thus accounting for lesion findings) but share resources involved in online syntactic processing (accounting for overlapping activation in imaging data and behavioral interactions), a hypothesis known as the *shared syntactic integration resource hypothesis*, or SSIRH. Support for this idea has been borne out in behavioral and electrophysiologial paradigms (Fedorenko et al., 2009; Hoch, Poulin-Charronnat, & Tillmann, 2011; Koelsch, Gunter, Wittfoth, & Sammler, 2005; Koelsch & Siebel, 2005; Koelsch & Friederici, 2003; Koelsch, Gunter, Friederici, & Schröger, 2000; Koelsch, Rohrmeier, Torrecuso, & Jentschke, 2013; Slevc, Rosenberg, & Patel, 2009; review: Kunert & Slevc, 2015). An early right-anterior negative ERP component (ERAN) occurring around 150–250 milliseconds after chord onset has been shown to be a hallmark of these musical syntactic violations (Koelsch & Friederici, 2003; Koelsch, 2005; Koelsch et al., 2000; Koelsch et al., 2013). This ERP component is similar to (Koelsch & Friederici, 2003; Koelsch, 2005) and even interacts with (Koelsch et al., 2005) anterior negative ERP components elicited by linguistic syntactic manipulations. Note, that these early negativities are characterized by hemispheric dominance, but not exclusivity. A similar pattern of results was echoed in an intracranial EEG study conducted by Sammler and colleagues (2012). Syntactic violations in music and language exhibited significant (but not complete) overlap among frontal and temporal electrodes, bilaterally.

Musical violations tended to generate more activity in frontal electrodes, while linguistic violations produced more activation in temporal lobes, which did not respond to musical syntactic violations. Additionally, language-related responses peaked earlier among left-hemisphere sites, while music-related responses peaked earlier in the right hemisphere.

However, some of these interactions may be highly task-dependent (LaCroix et al., 2015). In conflict with the SSIRH, fMRI work by Fedorenko and colleagues (Fedorenko et al., 2011; Fedorenko et al., 2012) indicates that when controlling for low-level processing aspects of language (via sentences vs. strings of pronounceable nonwords to control phonological processes) and music (via recordings of songs vs. rhythm- and pitch-scrambled versions to control rhythm- and pitch-extraction processes), individually defined regions of interest (ROIs) for either language or music showed little activity in response to changes in the other domain when processing higher-level features, like syntax. Finally, Farbood, Heeger, Marcus, Hasson, and Lerner (2015) directly examined fMRI activations and inter-subject response correlations between larger-scale hierarchical scrambling manipulations of a musical piece at the level of measures, phrases, and sections. This activity was compared with a verbally delivered narrative, also hierarchically scrambled at the word, sentence, and paragraph level (Lerner, Honey, Silvert, & Hasson, 2011). They found that more primary, acoustically sensitive auditory areas (the bottom of the hierarchy) were sensitive to all levels of scrambling in both domains, but higher-level structure in music engaged regions extending across middle superior temporal gyrus into frontal cortex. This pattern was distinct from the areas sensitive to higher-level structure in linguistic scrambling, which progressed more posteriorly, into the temporoparietal junction and more anterior frontal areas.

Another fMRI study by Rogalsky and colleagues (2011) compared music with speech and scrambled speech and demonstrated that areas sensitive to the structural manipulations in the linguistic stimuli were dissociable from voxels responsive to musical stimuli. These authors, along with Slevc and Okada (2015), suggest that evidence of overlap between music and speech processing may in fact be due to a mutual reliance on domain-general cognitive resources such as working memory or cognitive control. Support for this hypothesis comes from evidence for overlapping regions of cortex in left inferior frontal gyrus that are activated both by cognitive control tasks and linguistic syntax processing (Hsu, Novick, & Jaeggi, 2017; January, Trueswell, & Thompson-Schill, 2008). Complementary support for this idea comes from findings that harmonic violations in music and syntactic violations in language interact and drive left inferior frontal gyrus activation (Kunert, Willems, Casasanto, Patel, & Hagoort, 2015), suggesting that cognitive control resources may be engaged in the resolution of both violations. Although the relationship between cognitive control and syntactic violations requires further study, it is worth noting that prefrontal areas implicated in cognitive control are also implicated in other fMRI data that find parallels in the processing of language and music (Janata et al., 2002; Koelsch et al., 2002; Oechslin et al., 2013).

Semantics

Semantic processing is integral to all linguistic operations. It allows us to identify and name referents or ideas when communicating. However, an analog is difficult to place in the musical domain, given that communication through music does not typically rely on conveying referential information (Slevc & Patel, 2011). In language, semantic information partially involves object, sensory, and referential knowledge about a given word, which can be decoded from distributed activation patterns in the brain (Carlson, Simmons, Kriegeskorte, & Slevc, 2014; Correia et al., 2014; Mitchell et al., 2008; see, in this volume, Bauer & Just, Chapter 21, and Musz & Thompson-Schill, Chapter 22). The left anterior temporal pole may function as a hub that connects and activates individual representations (Correia et al., 2014). This hypothesis is strongly supported by work on semantic dementia, which involves the progressive loss of the ability to name objects in the environment and is associated with degeneration of the anterior temporal lobe (Patterson, Nestor, & Rogers, 2007). Importantly, semantic knowledge also includes more abstract, conceptual components that cannot map directly onto objects or bodily experiences, which is supported by a larger network that includes angular gyrus, fusiform gyrus, inferior frontal gyrus, middle temporal gyrus, posterior cingulate gyrus, superior frontal gyrus, supramarginal gyrus, and ventromedial prefrontal cortex (Binder & Desai, 2011). Huth, de Heer, Griffiths, Theunissen, and Gallant (2016) conducted a comprehensive examination of long passages of natural speech using voxel-wise model estimation that predicts activity of individual voxels following a given word by its co-occurrence with all of the words in a large corpus of English. The general semantic areas implicated in previous work were again identified using this method. Principal component and clustering analyses also uncovered 12 main semantic categories in the neural activation patterns. These could be mapped back onto the surface of the brain, creating an atlas of where activation for each word resided. The results showed that category-related words in the stimulus set clustered together, and that these representations were consistent across individuals.

Impressive decoding efforts like those just described would be difficult to instantiate in musical stimuli; however, there is some indication that musical knowledge can access this same general semantic network. Koelsch and others (2004) took advantage of the well-known N400 ERP response that is a hallmark of semantic integration difficulty, exhibiting higher amplitudes when words or concepts are out of place in a given referential context (Kutas & Federmeier, 2011; Lau, Phillips, & Poeppel, 2008). They utilized a semantic priming paradigm, wherein a short sentence describes a situation and is followed by a word, which may or may not fit the context of the sentence. When the context did not fit, EEG activity 400 milliseconds after word onset tended to be stronger than for words that were more appropriate. The key manipulation in this study, however, was that some target words were preceded by musical sequences that resembled objects or established a connotative context, such as for "wideness," "stairs," or "bird." Target words that did not match the context set up by the preceding musical sequence exhibited an N400 effect similar to the linguistic trials, demonstrating that a semantic context was recalled and established by the musical sequence.

This clever design establishes that semantic knowledge can interface with musical stimuli, but this interaction likely does not possess the richness of meaning that a sentence might. More importantly, the constituent parts in the musical sequences (notes and chords) themselves have little to no specific semantic meaning for most listeners in the same way that each word in a sentence does. Thus, the connotative meaning of the sequence requires more time to be built up, and would be difficult to manipulate on a finer level. Musical processing also appears to be preserved in some cases of semantic dementia (Weinstein et al., 2011), suggesting that musical concepts are dissociable from the processes with which the anterior temporal lobes are involved.

Perhaps a more interesting musical parallel to linguistic semantics is absolute pitch. Absolute pitch is the rare ability to name individual notes without a tonal reference (Siegel & Siegel, 1977a; Miyazaki, 1988). This is thought to be due to a proficiency in labeling abilities, as absolute pitch participants easily provide the nearest categorical note name to a tone that might vary continuously throughout the frequency spectrum (Levitin & Rogers, 2004). Notably, however, there are indications they do not *perceive* the notes categorically in the same way that variability around anchors in speech categories is ignored (Levitin & Rogers, 2004); that is, they provide poorer goodness of fit ratings as frequencies move from tonal centers, and have the same frequency-difference detection thresholds as other non-absolute pitch possessors. Thus, these individuals have the ability to map the sound of the note to its semantic label readily, despite small deviations in frequency, similar to how listeners provide the name of a word following an appropriate acoustic pattern. Given that this ability is particular to the 12-pitch chroma that make up Western music, this could provide an interesting avenue to test lexical or semantic access with a reduced dimensionality compared to that of a lexical or semantic knowledge database.

Rhythm

Music and language unfold over time as highly structured sequences. The temporal nature of both domains requires the orchestration of a wide variety of neural and cognitive processes in both the producer of the sequence (be it a melody or sentence) and the listener (Janata & Grafton, 2003). Regularity in the timing of these sequences helps align the systems of both the transmitting and receiving ends of the communication by directing attention to certain points in time to help create expectations and predictions. These anticipatory processes, in turn, help to guide attention, and to coordinate actions and movements in response. How quickly does such activity need to occur? A review of a large corpus of speech and music by Ding and colleagues (2017) suggests that there are regularities in the rates at which music and speech unfold in time. Musical information typically unfolds at a rate of about 2 Hz, while speech unfolds somewhat more rapidly at 5 Hz.

The regularities observed across such a wide array of stimuli may be a function of the perceptual or neural constraints on the part of the interlocutors. Indeed, MEG findings suggest that low-frequency neural oscillations (< 8 Hz) in the delta (1–3 Hz) and theta (4–8 Hz) bands are involved in entrainment to musical (Doelling & Poeppel, 2015) and linguistic information (Ding et al., 2015). This aligns closely with the temporal regularities indicated in the stimuli just described. An influential hypothesis (Giraud & Poeppel, 2012) suggests that neural oscillations at these rates are responsible for packaging or chunking incoming information, which in turn allows for an alignment between the neural system and the stimulus as a given communication unfolds in time, perhaps by driving or realigning gamma (25–35 Hz) band activity, which is thought to be related to attention (Griffiths et al., 2010; Mesgarani & Chang, 2012; Zion Golumbic et al., 2013).

There are also important differences between music and speech in the role that rhythm plays. Rhythmic information in speech is used for prosodic cues, to convey metrical stress as well as for differentiating phonological cues, such as voice onset time (Patel, 2012), which may operate at the level of syllables (Ghitza, 2012). However, these rarely evoke a regular pulse in the same way that musical rhythm does (Patel, 2006). Beta band activity (around 20 Hz, notably distinct from the ranges just mentioned) has been found to track the rhythmic regularity of an incoming stimulus in a predictive manner (Fujioka, Trainor, Large, & Ross, 2012), while gamma activity appears to follow the metrical regularity as it is internally represented (Fujioka, Trainor, Large, & Ross, 2009; Large & Snyder, 2009). This was demonstrated in an MEG study where a small number of tones in a sequence that demarcated an isochronous rhythm were removed. Regular beta activity tracked with inter-beat intervals and was disrupted by the missing tones, while gamma activity tracked the regularity of the sequence, regardless of the missing tones (Fujioka et al., 2009).

The relationship between beta band activity and music, as well as between beta range activity and movement more generally (Hari & Salmelin, 1997), underscores another major difference between speech and musical processing: musical rhythm is often associated with (sometimes spontaneous) motor activity such as foot tapping, head nodding, and dancing (Janata & Grafton, 2003; Patel, 2006); that is, the regularity found in musical rhythm supports and encourages synchronous movements to a beat. Accordingly, it has been found that the processing of musical rhythms engages sensorimotor structures in the brain such as the supplementary motor area, premotor cortex, cerebellum (Chen, Penhune, Zatorre, 2008a, 2008b; Janata & Grafton, 2003), and basal ganglia (Grahn, 2009; Grahn & Brett, 2007; Grahn & Rowe, 2009). Notably, many of the studies demonstrating the engagement of motor areas during rhythm perception typically involve passive listening rather than overt movements (Chen et al., 2008a; Grahn & Rowe, 2009) and are similar to the areas involved in perceiving speech rhythms (Geiser, Zaehle, Jancke, & Meyer, 2008). Moreover, these areas often display a large degree of functional connectivity during rhythm perception, which can be modulated by beat strength (Grahn & Rowe, 2009)

Finally, the strong proclivity for humans to move rhythmically to music is something of an anomaly in the animal kingdom, as most animals, including our close primate relatives, do not entrain to external rhythms (Patel, 2006). Why are humans capable and inclined to move synchronously to rhythms? One hypothesis, known as the *vocal learning and rhythmic synchronization hypothesis* (Patel, 2006), suggests that the ability to entrain and move to a beat is related to the need to learn the vocalizations of one's species. Specifically, the control required to direct and refine vocalizations establishes connections between auditory and motor areas in the brain that support movements based on acoustic input. Evidence in favor of this hypothesis comes from examples of animals such as the cockatoo (Patel, Iverson, Bregman, & Schultz, 2009a; Schachner, Brady, Pepperberg, & Hauser, 2009), which can spontaneously produce accurate, sustained movements in time with music (Patel, Iverson, Bregman, & Schultz, 2009b). Note, however, that there is emerging evidence that a non-vocal-learning species can be trained to follow a beat (Takeya, Kameda, Patel, & Tanaka, 2017; Wilson & Cook, 2016), so more work is needed to understand the processes underlying rhythmic entrainment.

Conclusions and Future Directions

It is perhaps no surprise that, as acoustic signals, music and language tread much the same ground as they ascend the auditory pathway from the brainstem to primary auditory cortex and beyond. This is emphasized by the less obvious and quite interesting evidence that long-term experience can, in some cases, induce plastic changes in neural function and even in cortical structure in parts of auditory cortex, motor cortex, and corpus callosum. As to how experience might induce these changes, the OPERA hypothesis suggests that sustained top-down attention, repetition, and motivation in a precise task, required by either music or language experience, could play a prominent role in modifying neural circuitry shared by both domains (Patel, 2011, 2012, 2014). However, in higher areas of cortex, certain processes appear to become more specialized for each domain and are influenced by other cognitive functions. Overlap in linguistic and musical neural processing is less clear at these stages, with quite disparate neural resources engaged by each domain in many cases. Picking apart where operations between domains do and do not overlap is an active area of research and debate. Given the evidence of positive, cross-domain behavioral outcomes associated with neural plasticity induced by long-term experience in the brainstem, identifying higher neural regions and cognitive operations that could be improved by musical training is an exciting possibility. However, a limiting factor beyond auditory cortex appears to be the often inconsistent evidence for overlap in the neural structures involved in processing music and language. Based on evidence reviewed here, more work is needed to clarify more precisely which higher linguistic and cognitive functions might be candidates for improvement via cross-domain experience and plasticity. As others have pointed out (Patel, 2006, 2012), one promising possibility for future research will be to investigate the possibility of overlapping rhythmic processes between music and language (Doelling & Poeppel, 2015).

This search may be hampered by the level of resolution that is currently available among the methods in our toolbox. EEG, MEG, and fMRI have proven invaluable, but as Peretz and colleagues (2015) have pointed out, it remains possible that "overlap" in these studies may reflect domain-specific networks that overlap *geographically* (at least within the spatial resolution of a given method) but do not interact *functionally*. For example, activation of a given voxel or region when listening to speech could be the result of speech-related neural computations by a few thousand of the many thousands of neurons represented by that voxel. A similar level of activation may also be found for that voxel when performing a music-related task; however, this could be the result of activity within the same few thousand neurons, or a completely *different* set of neighboring neurons. Resolving issues like this in fMRI is quite difficult, although new data-driven methods may provide some solutions (Norman-Haignere et al., 2015), as will future, cleverly designed studies perhaps aided by interference paradigms (Kunert & Slevc, 2015). ECoG might be another useful tool for resolving these issues. While this method has been very profitably employed for phonological (Chang et al., 2010; Mesgarani et al., 2014), syntactic (Ding et al., 2016), and streaming investigations (Mesgarani & Chang, 2012; Zion Golumbic et al., 2013) in speech, there are only a handful of studies employing this technique to examine musical sequences (Potes et al., 2012, Potes, Brunner, Gunduz, Knight, & Schalk, 2014; Sammler et al., 2012; Sturm et al., 2014). It will be very interesting to see what is revealed about the processing of music, speech, and the auditory system as musical ECoG work develops. Studies of attention-modulated cortical activity in ECoG, MEG, or EEG may particularly benefit from examining an acoustically rich, multi-part stimulus like music. Additionally, employing stimulus reconstruction techniques in these studies could be particularly illuminating for the cognitive aspects of streaming operations and attentional processes that are engaged during music listening, especially given the use of timbre and timbral fusion as compositional tools (McAdams, 1982; McAdams & Bregman, 1979).

Another useful approach may be to focus on the more primitive cognitive or acoustical operations at play in both domains, similar to how linguists have re-examined concepts such as syntax (Ding et al., 2016; Fedorenko, Duncan, & Kanwisher, 2012), semantics (Binder & Desai, 2011; Lau et al., 2008), and phonology (Du et al., 2014; Scharinger, Idsardi, & Poe, 2011) through different sets of constituent cognitive operations. Music research in particular might benefit from this type of refinement and, indeed, work to catch up to language in this respect is underway (Parbery-Clark, Strait, Anderson, Hittner, & Kraus, 2011; Schulze & Koelsch, 2012; Slevc et al., 2016; Slevc & Okada, 2015). A better understanding of the acoustical analyses the brain engages in when perceiving timbre, which is perhaps the least understood aspect of music perception from a neural perspective, could shed better light on the acoustical operations common to both domains. Additionally, examining how music and language tasks might mutually or differently engage more primary executive functions such as conflict management, switching, and working-memory updating (Diamond, 2013; Miyake & Friedman, 2012) might indicate what operations are taxed by both domains and could better clarify previous findings (Kraus, Strait, & Parbery-Clark, 2012; LaCroix et al., 2015; Schulze & Koelsch, 2012; Slevc & Okada, 2015). Finally, our understanding of language and music will surely benefit from a better understanding of the neural processes involved in the *production* of language and music. So far, there has been relatively little work directly comparing speech and music production or improvisation (e.g., Brown, Martinez, & Parsons, 2003; Callan et al., 2006; Zarate, 2013); however, insights from production are likely to be informative for both domains.

While the relationship between music and language is still a somewhat controversial topic (e.g., Heffner & Slevc, 2015; Leaver & Rauschecker, 2010; Norman-Haignere et al., 2015; Patel, 2012; Peretz et al., 2015; Schellenberg, 2015; Slevc & Okada, 2015), it is clear that fundamental similarities in early stages of processing provide a foundation for cross-domain modulation by long-term musical and linguistic experience. The overlap observed at earlier stages of processing appears to give way to greater neural specialization at higher levels of cortex, which might preclude any cross-modal experience-dependent plasticity (Patel, 2012). Thus, whether similar interactions resulting from the plastic effects of experience in one domain or the other are indeed present at higher levels remains to be seen. To resolve these issues, a deeper understanding of the neural mechanisms involved in perceiving and processing music is needed, which, in turn, will likely illuminate and motivate new hypotheses on aspects of speech processing, auditory processing, and the cognitive operations that support these two fundamental faculties that color and enrich the human experience.

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